

A Case of Alpha-Fetoprotein-Producing Gastric Cancer

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Abstract

Introduction: A case of alpha-fetoprotein (AFP)-producing gastric cancer is described in a 57-year-old Chinese woman. **Clinical Picture:** She presented with bleeding tendency and bone pain, and was found to have haematological evidence of disseminated intravascular coagulation and spinal metastasis. Her tumour markers, including AFP, Ca 19-9 and carcinoembryonic antigen (CEA) were elevated. In view of the elevated tumour markers, there was an exhaustive search for a primary lesion in the gastrointestinal tract, liver and ovaries. There was no radiological evidence to suggest any lesion in the chest, liver or pelvis. Lectin affinity electrophoresis of the AFP showed AFP-L2 and AFP-L3 bands, which are suggestive of a non-hepatoma malignancy. **Management:** Gastroscopy showed a gastric ulcer and she developed bleeding after the gastric biopsy which required urgent surgery. Intraoperatively she was found to have carcinomatous peritonei and a malignant ulcer in the greater curve of the stomach. Histology confirmed a linitis plastica like adenocarcinoma which stains for AFP. **Outcome:** She died from multi-organ failure 3 days after surgery. **Conclusion:** AFP-producing adenocarcinoma of the stomach is not uncommon. Lectin affinity electrophoresis of AFP is helpful in the differentiation between hepatoma and non-hepatoma malignancies.

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Key words: Gastric adenocarcinoma, Lectin electrophoresis, Tumour markers

Case Report

A 57-year-old accountant presented to her doctors in a neighbouring country in early October 1998 with problems of easy bruising, bleeding gums, one single episode of gross haematuria and 2 months of back pain. Investigations showed evidence of disseminated intravascular coagulation (DIVC) and compression fracture of T10 vertebra. She was given antibiotics, fresh frozen plasma and steroids. She came to Singapore for further evaluation on 10 October 1998.

On systems review, she also complained of intermittent dyspepsia and abdominal distension. She had significant weight loss of 7 pounds over the preceding 2 months. She also experienced episodic night sweats and fever.

Clinical examination was essentially normal except for an unremarkable enlarged soft left supraclavicular lymph node and a 1-cm nodule on the right chest wall. Breasts, per rectal and per vaginal examinations were also normal.

Significant investigations that were done are summarised below.

Full blood count showed evidence of mild anaemia, haemoglobin (Hb) was 8.6 g/dL, total white (TW) count of $11.4 \times 10^9/L$ and platelets (Plt) count of $119 \times 10^9/L$. A few days later her full blood count showed evidence of a leukoerythroblastic picture [TW was $21.5 \times 10^9/L$, polymorphs 74%, lymphocytes 12%, monocytes 6%, normomyelocytes 8% and nucleated red blood cells were 5/100 white blood cells]. Her initial tests done in the neighbouring country suggested DIVC; fibrinogen <0.93 g/L (2-4) and fibrin degradation products were elevated.

She had elevated serum tumour markers, CA12-5 was 42.5 U/mL (0-35), CA19-9 was 2123 U/mL (0-36), carcinoembryonic antigen (CEA) 1223 U/mL (0-3.5), alpha-fetoprotein (AFP) 885 U/mL (1-10), repeated 1070 U/mL, lactate dehydrogenase (LDH) 1253 U/L (180-380) and CA15-3 was normal at 13.0 U/mL. The elevated tumour

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markers, namely CEA, CA19-9 and AFP suggested a possibility of a primary tumour in the gastrointestinal tract, liver or ovaries and a search for a primary in these areas was initiated.

Liver function tests were: total protein 73 g/L, albumin 45 g/L, bilirubin 8 μ mol/L, alkaline phosphatase (ALP) 568 U/L, alanine transaminase (ALT) 35 U/L, aspartate transaminase (AST) 44 U/L and heat stable ALP 78 U/L. The elevated serum ALP picture was consistent with bony involvement. Her hepatitis markers, in particular hepatitis B and C, were negative. Lectin affinity electrophoresis of AFP showed the presence of AFP-L2 and AFP-L3 fractions suggestive of a non-hepatoma origin (Fig. 1).

Computed tomographic (CT) scan of the abdomen showed multiple para-aortic lymph nodes with mild right hydronephrosis. There was a small space-occupying lesion within the dilated right renal pelvis. Possibilities were blood clots or neoplasm. Bilateral pleural effusions and lower lobe consolidations were noted. The liver was normal.

CT pelvis and renal angiogram were normal.

Bone scan showed multiple metastases in the axial skeleton over the skull vault, thoracolumbar spine, bilateral ribs and the pelvis. X-ray of the thoracolumbar spine revealed destruction of pedicles of the T10 vertebra. Magnetic resonance imaging (MRI) of the thoracic spine showed thoracic spine metastases involving T3, T8, T9 and T10 vertebral bodies with cord compression in multiple levels at T9, T10, T11 and T12 vertebral bodies.

Fine needle biopsy of the lump on the chest wall had an inconclusive paucicellular yield. Urine for cytology was negative for malignant cells. Bone marrow aspiration and trephine biopsy (24 October 1998) were done in view of leukoerythroblastic blood picture. This showed metastatic adenocarcinoma.

Gastroscopy was performed on 20 October 1998 in view of dyspepsia. There was a gastric ulcer in the body of the stomach. This appeared benign to the endoscopist performing the gastroscopy. However, she developed severe gastrointestinal bleeding after the gastroscopy. Her haemoglobin fell from 9.8 g/dL to 5.4 g/dL despite repeated blood transfusions. A repeat gastroscopy was done on 23 October 1998 and there was a gastric ulcer with active bleeding. An emergency laparotomy was performed and intraoperatively, there was a malignant looking ulcer measuring 2 by 1 cm in the greater curve of the stomach penetrating the serosa with carcinomatous peritonei. The pancreas was bulky and the liver was clear. There was mild ascites. She underwent a palliative ulcerectomy (excision of the ulcer).

Histology of the resected specimen showed a poorly differentiated adenocarcinoma with extensive tumour

necrosis. The neoplastic cells were small and proliferate as microaggregates, penetrating the connective tissue, smooth muscle bundles and infiltrating into the serosal surface (linitis plastica like growth pattern). Venous and lymphatic tumour emboli were found. The tumour cells expressed AFP. All vascular and adipose tissues and small lymph nodes (5/5) contained metastatic carcinoma (Figs. 2 & 3).

Progress

She remained ill after her operation, with clinical and biochemical evidence of DIVC requiring blood and plasma product support. She developed adult respiratory distress syndrome on the third postoperative day. Her condition deteriorated and she passed away on that same day.

Discussion

This patient presents with an AFP-producing gastric carcinoma and histologically staining positive for AFP with no hepatoid differentiation. She had metastases to the bone, bone marrow and the peritoneal cavity. She had elevated tumour markers, namely, AFP, CA19-9 and CEA suggestive of a primary in the liver, gastrointestinal tract or ovaries. Lectin affinity electrophoresis showed the presence of AFP-L2 and AFP-L3 bands suggestive of a non-hepatoma origin. She died from complications related to her disease, mainly DIVC. As non-hepatoid AFP staining and AFP-producing gastric carcinoma is infrequently encountered in our practise, the subsequent discussion will centre on this topic.

AFP is an oncofetal glycoprotein measuring 70,000 dalton. It has a structural homology with human albumin.¹ It is made by human yolk sac cells and later in embryonic growth, by the fetal liver which, as it matures, switches its protein production to albumin.¹ Elevated levels are correlated with various fetal abnormalities such as anencephaly and open neural tube defects.¹ The subtypes of AFP in the above situations have not been defined. AFP was found to be a marker for malignant diseases. The highest levels occur in germ cell tumours, hepatomas, tumours of the gastrointestinal tract and in children, hepatoblastoma. It is still not known why tumours secrete AFP.¹ Suggestions of dedifferentiation in the tumours were raised.

Microheterogenities in AFP with the carbohydrate moieties varying from different sources have been exploited to distinguish primary hepatic carcinoma from other tumours and other benign liver diseases.¹⁻³

Taketa et al² have shown the promise of using lectin affinity electrophoretic separation of AFP in the differentiation between chronic hepatitis and liver cirrhosis from hepatoma. Lectin affinity electrophoretic separation of AFP was carried out using AFP differentiation kits

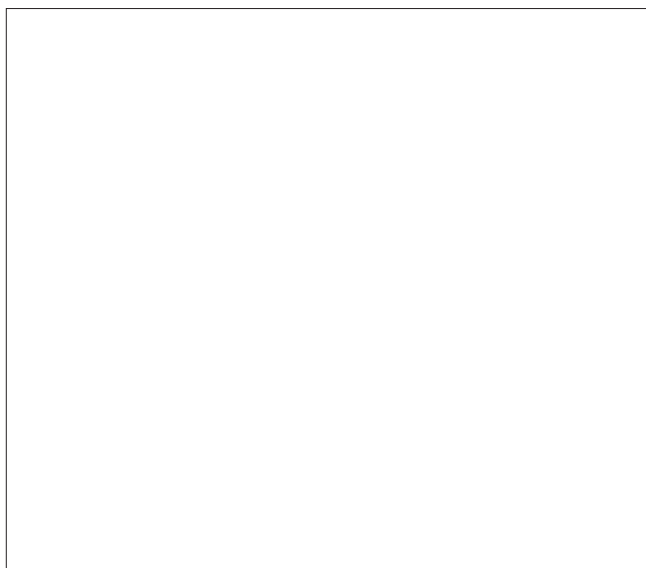


Fig. 1. Lectin electrophoresis of this patient demonstrating the presence of L2 and L3 bands.

which used *Lens Culinaris* agglutinin-A (Kit L) and erythroagglutinating phytohaemagglutinin (Kit P). Separated AFP bands were detected with a sensitive antibody-affinity blotting technique and determined quantitatively by densitometry, and the results were expressed as percentages of the intensity of the total AFP bands. They reported that the presence of AFP-L3 and AFP-P4+P5 concurred sensitivities of 55.3% and 61% and specificities of 93.9% and 82.3% respectively in favour of hepatoma. Although the sensitivity is not optimal, AFP-L3 is highly specific for hepatoma. They also noted that AFP-L2 was observed in yolk sac tumours and gastrointestinal tumours.

Shimizu et al³ described and discussed the performances of new AFP microheterogeneity assay kits, based on differences in their affinity for lectins in 55 patients with elevated AFP. In particular, the L3 band was specific for hepatoma and the presence of the L2 band suggested the presence of other tumour types.

Our patient demonstrated the presence of elevated AFP-L2 band suggesting the presence of either a yolk sac tumour or a gastrointestinal tumour, and was later found to have stomach cancer. We plan to conduct more studies to validate the above observations in our local population.

AFP-producing gastric carcinomas had been reported previously in other case series.⁴⁻⁸ It was first reported in 1970.⁴ The incidence varied from 1.3% to 15% depending on the series. It is positive in about 3.9% to 5% of gastric cancer patients in Japan.⁵⁻⁷ Chang et al⁵ found 24 cases of AFP-producing gastric carcinoma out of 556 gastric carcinoma patients over a 10-year period (4.3%). When compared with all other cases of gastric cancer, AFP-

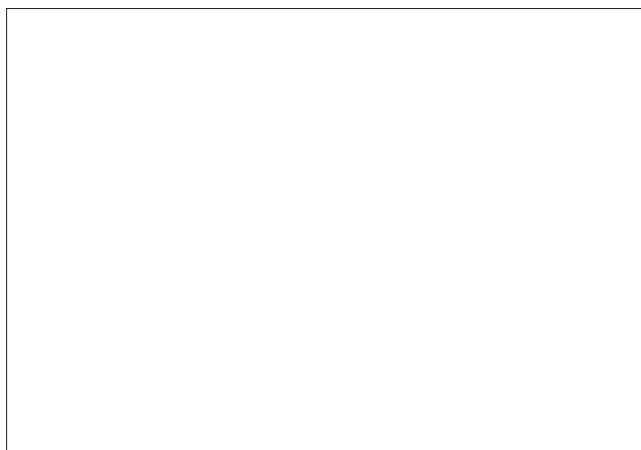


Fig. 2. Histology of the resected specimen shows a poorly differentiated adenocarcinoma (Magnification x100, haematoxylin & eosin stain).

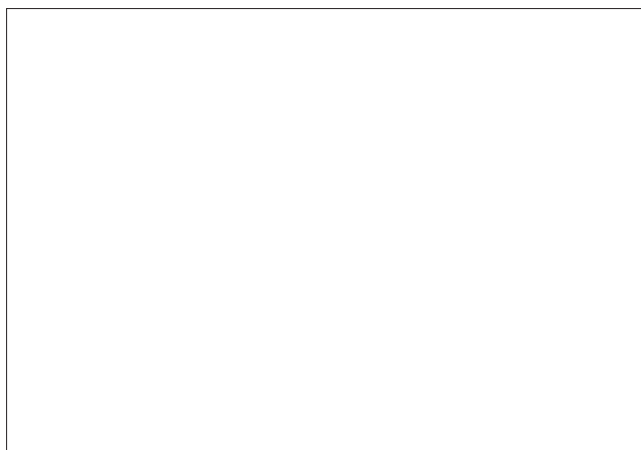


Fig. 3. AFP-stained positive cells (in brown, immunoperoxidase stain) in a higher magnification (x200) of above slide.

producing cancers have higher incidences of lymph node metastasis, lymphatic and venous invasion of the gastric wall, liver metastasis, low radical resectability and poorer prognosis.⁵⁻⁹ Motoyama et al¹⁰ proposed that AFP-producing gastric cancers be divided into 3 pathological subtypes, mainly hepatoid type, yolk-sac tumour type and the fetal gastrointestinal type. The hepatoid subtype was the most common type of AFP-producing gastric cancer and had the worst prognosis.

The prognosis of AFP-producing gastric cancer is poor and the 5-year survival rate post curative resection has been reported to be only 8.3%.^{5,6} Koide et al⁹ studied the tissue samples from 4 patients with AFP-producing gastric cancer and compared them with 26 cases of AFP-negative gastric cancer histochemically to determine the malignant potential in terms of cell proliferation, apoptosis and angiogenesis. They concluded that AFP-producing gastric cancers have high malignant potential, with high proliferative activity, weak apoptosis, and rich neovascularisation compared to AFP-negative gastric cancers. These biological

characteristics of AFP-producing gastric cancer reflect the aggressive behaviour and the poor prognosis of patients with this type of cancer.

Many different genetic alterations have been reported in gastric carcinoma, namely alterations of p53, CD44, c-met, c-erb2, k-sam, Ki-67, nm23 etc.¹¹⁻¹⁵ Overexpression and or gene amplification of c-met (a family of tyrosine kinase growth factor receptor) in patients with gastric cancer was found to be significantly correlated with depth of tumour invasion and lymph node metastasis and poorer prognosis in a study by Nakajima et al.¹² Amemiya et al¹³ evaluated 26 patients with AFP-producing gastric cancer with 26 stage matched controls for c-Met, hepatocyte growth factor (HGF) expression and proliferating cell nuclear antigen labelling index using immunohistochemical analysis. A significantly higher frequency of c-Met expression was observed in the AFP-positive group ($P < 0.01$). This could explain for the poorer prognosis of AFP-producing gastric cancers.

Kumar Dhar et al¹¹ looked at nm23 overexpression in AFP-producing gastric carcinoma. The nm23 gene is thought to be a metastasis suppressor gene, and low nm23 expression has been reported with unfavourable prognosis in patients with breast, hepatocellular, prostate and gastric carcinoma.¹⁶⁻¹⁹ In contrast to earlier studies, Kumar Dhar et al found that overexpression of nm23 was associated with shorter overall survival, local tumour invasiveness, tumour progression and distant metastasis. They studied 30 patients with AFP-producing gastric cancer and compared with 29 randomly selected matched controls of non AFP-producing gastric cancer with regards to overexpression of nm23. Overexpression of nm23 was not significantly different between the two groups.

In conclusion, AFP-producing carcinomas are not that uncommon, more biological studies, as well as precise criteria for pathological subclassification and therapy are still necessary for a better understanding, and hopefully better management of this entity.

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