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Gastric Hepatoid Adenocarcinoma

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Abstract

Gastric Hepatoid AdenoCarcinoma (GHAC) is a special type of gastric cancer characterized by morphological features similar to hepatocellular carcinoma (HAC). GHAC has been found in different organs such as the stomach, lung, pancreas, oesophagus, papilla of Vater, colon, kidney, uterus and peritoneum. The diagnosis of GHAC is not dependent on production of AFP, but mainly based on recognition of characteristic histologic features. We report the case of a 72-year-old male patient who underwent a total gastrectomy for a large poorly differentiated gastric tumour. The microscopic examination of the tumour showed an adenocarcinoma with two distinct patterns: that of an adenocarcinoma with glandular differentiation and another with a morphological pattern consisting of polygonal neoplastic cells with abundant eosinophilic cytoplasm, prominent nuclei and high mitotic activity. Immunohistochemical staining revealed positive Hep Par1 and AFP, while CK7 and CK20 were negative, the percentage of hepatoid differentiation being about 60%. On the basis of histological and immunohistochemical findings, the diagnosis of hepatoid gastric adenocarcinoma was established. In general, GHACs have an unfavourable prognosis. The majority have already metastasized by the time of diagnosis, usually to the liver and lymph nodes.

Key words *Gastric Cancer, Hepatoid Adenocarcinoma, AFP, Hep- Par 1, Immunohistochemistry*

Introduction

Hepatoid adenocarcinomas belong to a rare group of extrahepatic tumours that show liver differentiation and produce A-Fetoprotein [1]. AFP-producing gastric tumours were first described by Bourreille in 1970 [2]. Later, Kodama *et al* described two histological types of AFP-producing gastric carcinomas: a well-differentiated papillary or tubular type and a medullary type which is characterized by polygonal cells arranged in solid nests or sheets with scattered large pleomorphic or multinucleated giant cells [3].

Finally, in 1985 Ishikura *et al* proposed the term "Hepatoid adenocarcinoma (HAC) of the stomach" for primary gastric carcinoma characterized histologically by hepatoid differentiation and significant production of AFP [4]. However, he noticed that there are cases of primary AFP-negative gastric carcinomas with characteristic histologic features mimicking hepatocellular carcinoma [5].

We present a case of hepatoid adenocarcinoma of the stomach which was confirmed by immunohistochemical staining.

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Case presentation

A 72-year-old male patient presented with dyspeptic symptoms of four months duration. There was no documented weight loss, and the clinical examination revealed no abnormality. Haematological investigations revealed anaemia [haemoglobin 8,2g/dl, haematocrit (Ht) 27%]. Liver function tests, urea, and electrolytes were within normal range. Serological test for hepatitis B surface antigen and antibody and hepatitis C antibody were negative. AFP was significantly elevated (2500ng/ml), but CEA and Ca 19-9 were negative. Chest and abdominal radiographs were negative. Abdominal computed tomography (CT) demonstrated a mass in the lesser curvature of the stomach, without any secondary metastases in the liver (Figure 1).

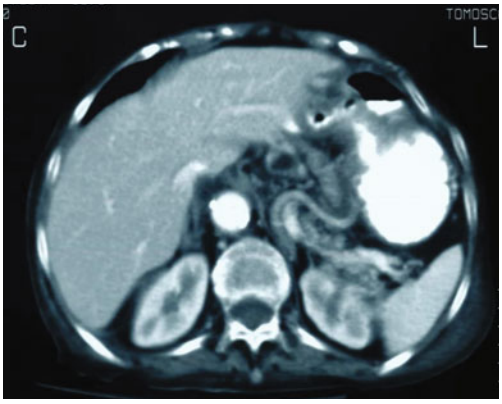

Figure 1. Abdominal computed tomography demonstrating a mass in the lesser curvature of the stomach, without any secondary metastases in the liver.

An upper gastrointestinal endoscopy showed an ulcerative central excavated gastric tumour mass with a mean diameter of 15cm. Biopsy showed "poorly differentiated adenocarcinoma". Total gastrectomy with a Roux en Y reconstruction was performed, and the resected specimen was sent for further histological examination.

The microscopic examination of the tumour showed an adenocarcinoma with two distinct patterns. The first was that of an adenocarcinoma with glandular differentiation (Figure 2a). The second morphological pattern consisted of polygonal neoplastic cells with abundant eosinophilic cytoplasm, prominent nuclei and high mitotic activity (Figure 2b). The neoplastic cells were arranged in a trabecular pattern. In these areas, the immunohistochemical staining revealed that HerPAr 1 (Figure 3a) and AFP (Figure 3b)

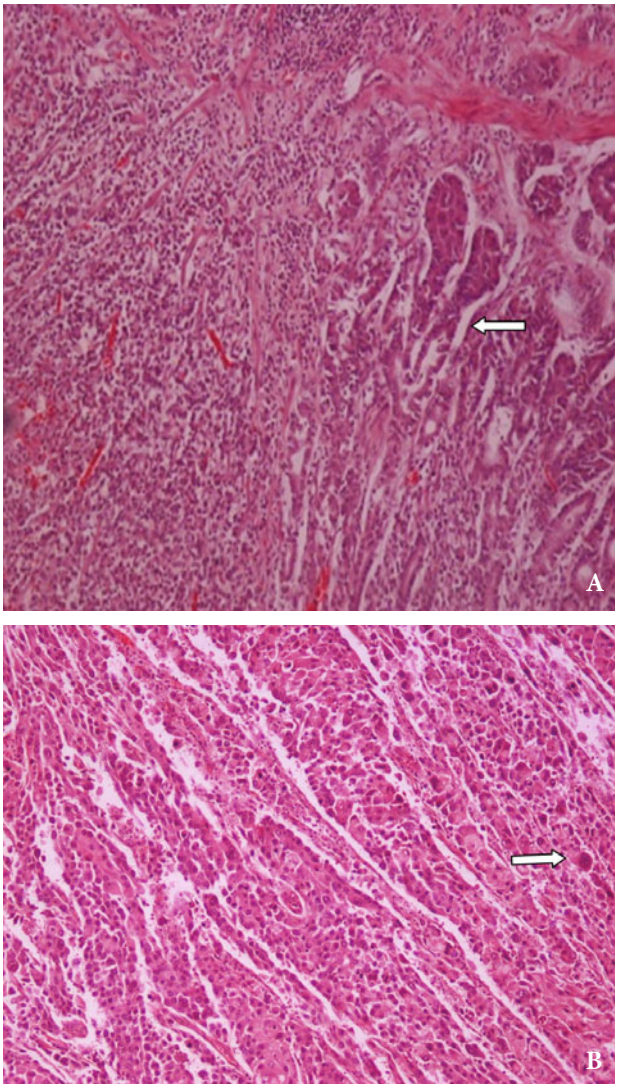

Figure 2. A) Poorly differentiated gastric cancer with glandular differentiation (H/E, x200). B) Poorly differentiated gastric cancer with hepatoid features (H/E, x200).

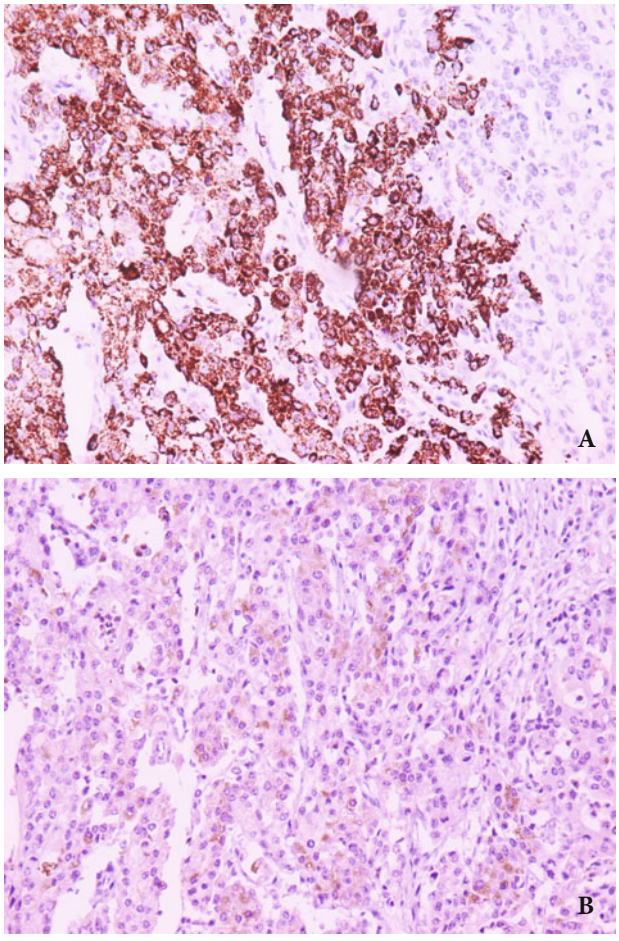

Figure 3. Immunohistochemical stains. A) The tumour cells show strongly positive reaction for Hep-Par1 (Hep –Par1 x200). B) The tumour cells show patchy, moderately positive reaction for alfa –fetoprotein (AFP, x200).

were positive, while CK7 and CK20 were negative. In the areas of glandular formations, the immunophenotype of neoplastic cells was reversed [HerPar 1(-), AFP (-) /CK7 (+), CK20 (+)]. These two patterns did not intermix with each other even though they did not have well-defined boundaries. The percentage of the tumour corresponding to hepatoid differentiation was about to 60%. On the basis of histological and immunohistochemical findings, the diagnosis of hepatoid gastric adenocarcinoma was established.

The neoplasm penetrated subserosal connective tissue without invasion of adjacent structures (pT3). Vascular invasion was observed. Regional lymph nodes assessment described 15 out of 21 lymph nodes with metastasis. At sites adjacent to the tumor, the gastric mucosa showed features of atrophic gastritis with foci of intestinal metaplasia (incomplete type).

The postoperative course was uneventful, and the patient was discharged 10 days after the operation. Adjuvant

chemotherapy was administered and 18 months later, the patient is disease-free and his tumour markers, abdominal CT scan and endoscopy are negative for any pathology. Written informed consent was obtained from the patient in order data be published.

Discussion

Gastric Hepatoid Adenocarcinoma (GHAC) is a rare but unique subtype of gastric cancer accounting for approximately 0.17% of all gastric malignancies [6]. These neoplasms can show elevated serum AFP of gastric production (primitive foregut origin), but there are cases where they show hepatoid differentiation without production AFP [4,5]. Hepatoid adenocarcinomas have also been reported in several different organs such as the lung, pancreas and ovary [7-9]. Most patients are of male gender, and the average age of presentation is 64 years. Although most symptoms are non-specific, epigastric pain and fatigue due to anaemia are not uncommon [6,10,11].

Macroscopically, these gastric tumours are large, nodular and polypoid. The most common primary sites are the antrum and the pylorus. Histologically, the tumour is composed of two closely related areas, a hepatoid-like area and an adenocarcinomatous one. The tumour cells in the former resemble the morphology of hepatocellular carcinoma (HCC) and immunohistochemically can be positive for AFP, alpha-1 antitrypsin (AAT), alpha-1 antichymotrypsin (ACT) and hepatocyte paraffin -1 (Hep-par1) [12].

The histogenesis of hepatoid adenocarcinoma remains a matter of debate. Many theories have been proposed, summarized as follows:

i. Ishikura *et al* have suggested that AFP producing gastric cancers are differentiated morphologically and functionally along with hepatocytes. This may be due to the fact that the stomach and liver both derive from the primitive foregut [3].
ii. It is known that hepatoid adenocarcinoma of the stomach nearly always expresses AFP, CEA, alpha-1 antitrypsin (AAT) and alpha-1 antichymotrypsin (ACT). Such markers of hepatocytic differentiation advocate that these hepatoid tumours arise from stem endodermal cells with a dual differentiation potential into either a hepatoid or a conventional intestinal cell line. Additionally, the presence of focal Hep-par1 reactivity in adenocarcinomas outside the liver, such as in our case, support that these hepatoid foci represent true hepatocellular differentiation. This finding is not surprising since the stomach is a foregut derivative [10,12].
iii. More recently, Kumashiro *et al* studied 23 cases of GHAC and 69 cases of non-Hepatoid Adenocarcinoma based on the immunohistochemical expression of gastric phenotype (CD10, MUC2, MUC5AC, MUC6) and CDX2 and indicated that no gastric phenotype was observed in any of the hepatoid component. Moreover, the authors showed CDX2 positivity in 51% of cases of GHAC; based on this finding, they proposed that hepatoid adenocarcinoma arises from an adenocarcinoma with intestinal phenotype and that its hepatoid component is in some way related to reduced CDX2 expression [13].

Primary GHAC has a poor prognosis because of frequent liver and lymph node metastases at the time of diagnosis that may be attributed to extensive venous involvement and production of AFP [6,11].

Treatment of GHAC is similar to that of gastric adenocarcinoma. Radical gastrectomy with appropriate lymphadenectomy carries a better prognosis at earlier stages and should be undertaken for advanced carcinomas when feasible. Adjuvant chemotherapy and radiotherapy should be administered according to current gastric cancer guidelines. Liver or lung metastasectomy of resectable lesions should be considered in all cases [10]. Palliative chemotherapy should be advised to all patients with advanced, non-operable, recurrent or metastatic gastric cancer and good performance status [14-16].

Conclusions

In conclusion, hepatoid adenocarcinoma of the stomach is a rare entity with a specific histological pattern and poor prognosis. The treatment of choice is similar to that for gastric cancer. We hope that in the future, the study of molecular markers for this type of cancer will help to provide an insight into its histopathogenesis and associated treatment modalities that will have a greater impact on patient survival.

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Ηπατοειδές Γαστρικό Αδενοκαρκίνωμα

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Περίληψη

Το ηπατοειδές γαστρικό αδενοκαρκίνωμα (ΗΓΑΚ) είναι ένας ειδικός τύπος γαστρικού καρκίνου που χαρακτηρίζεται από μορφολογικές ομοιότητες με το ηπατοκυτταρικό καρκίνωμα. Το ηπατοειδές αδενοκαρκίνωμα έχει ανευρεθεί σε διάφορα όργανα όπως ο στόμαχος, οι πνεύμονες, το πάγκρεας, ο οισοφάγος, το φύμα του Vater, το παχύ έντερο, οι νεφροί, η μήτρα και το περιτόναιο. Η διάγνωση του ΗΓΑΚ δεν βασίζεται στην παραγωγή α-εμβρυϊκής σφαιρίνης (AFP), αλλά κυρίως στην αναγνώριση των ιδιαίτερων ιστολογικών χαρακτηριστικών του. Παρουσιάζουμε την περίπτωση ανδρός 72 ετών που υποβλήθηκε σε ολική γαστρεκτομή για έναν ευμεγέθη γαστρικό όγκο με χαμηλή διαφοροποίηση. Η μικροσκοπική εξέταση του όγκου ανέδειξε ένα αδενοκαρκίνωμα με δυο ξεχωριστές μορφολογίες: εκείνη του αδενοκαρκινώματος με διαφοροποίηση των αδένων και μια άλλη με πολυγωνικά νεοπλασματικά κύτταρα με άφθονο ηωσινοφιλικό κυτταρόπλασμα, προεξέχοντες πυρήνες και υψηλή μιτωτική δραστηριότητα. Η ανοσοϊστοχημική χρώση ήταν θετική για HepPar 1 και AFP, ενώ τα CK7 και CK20 ήταν αρνητικά, με το ποσοστό της ηπατοειδούς διαφοροποίησης να φθάνει το 60%. Με βάση τα ιστολογικά κι ανοσοϊστοχημικά ευρήματα τέθηκε η διάγνωση του ηπατοειδούς γαστρικού αδενοκαρκινώματος. Γενικά, τα ΗΓΑΚ έχουν κακή πρόγνωση. Η πλειονότητα έχει εμφανίσει μεταστάσεις τη στιγμή της διάγνωσης, συνήθως στους λεμφαδένες και το ήπαρ.

Λέξεις κλειδιά *Γαστρικός καρκίνος, Ηπατοειδές αδενοκαρκίνωμα, AFP, Hep- Par 1, Ανοσοϊστοχημεία*

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