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Primary Gastric Choriocarcinoma With Paraneoplastic Hyperthyroidism:A Rare Case Report

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Abstract:*Primary Gastric Choriocarcinoma is an extremely rare entity, as the typical site for choriocarcinomais ovary or the testis. It is a highly aggressive tumour, accounting for only 0.08% of all gastric cancers. Most cases are misdiagnosed as adenocarcinomas initially or recognized very late in the course of the disease. A markedly elevated serum β-hCG and endoscopic biopsy that stains positive for β-hCG point to the diagnosis, though surgical excision and HPE of the entire specimen is needed for definitive conformation. Also, a markedly elevated β-hCG could lead to hyperthyroidism as there is cross reactivity to TSH receptor which stimulates production of thyroid hormones. This rare paraneoplastic presentation has not been reported in most case reports of Primary gastric choriocarcinoma.*
Here, we report a case of Multiple Liver Secondaries with manifest Hyperthyroidism which was eventually diagnosed as a Metastatic disease from a Primary Gastric Choriocarcinoma.
Key words:*Primary Gastric Choriocarcinoma, choriocarcinoma, paraneoplastic hyperthyroidism.*

I. Introduction

Primary Gastric Choriocarcinoma is an extremely rare entity, as most cases arise from ovary or the testis. It is a highly aggressive tumour, accounting for only 0.08% of all gastric cancers. Most cases are misdiagnosed as adenocarcinomas initially or recognized very late in the course of the disease. A markedly elevated serum β-hCG and endoscopic biopsy that stains positive for β-hCG point to the diagnosis, though surgical excision and HPE of the entire specimen is needed for definitive conformation. Metastasis to the liver and lung is very common. Hepatic failure and cancerous hemorrhage are the most common causes of death in these patients.

Also, a markedly elevated β-hCG could lead to hyperthyroidism as there is cross reactivity to TSH receptor which stimulates production of thyroid hormones. This rare paraneoplastic presentation has not been reported in most case reports of Primary gastric choriocarcinoma.

II. Case Report

We report a case of Multiple Liver Secondaries with manifest Hyperthyroidism which was eventually diagnosed as a Metastatic disease from a Primary Gastric Choriocarcinoma. The patient was a 62 yr old male who presented with upper abdominal pain and worsening general condition. On physical examination patient had fever, tachycardia, and was mildly icteric. Liver was palpable 6 cms below the costal margin, and was tender with irregular borders. External genitalia were normal. Though a provisional clinical diagnosis of Liver Abscess was made, USG &CT showed features of Multiple Liver Secondaries. Further evaluation with an esophagogastroduodenoscopy as part of the work-up, revealed an ulceroprolifirative lesion arising from the lesser curvature of the stomach. Multiple biopsies were taken, which showed features of choriocarcinoma and positive immunohistochemistry for HCG.

Biochemical work up revealed, β-hCG was grossly elevated >2lakh, with mild elevation of AFP and a normal CEA. A Scrotal USG ,to rule out primary choriocarcinoma in testis, was normal. A diagnosis of extra gonadal choriocarcinomaarising from the stomach was made. Also HCG-induced hyperthyroidism/thyrotoxicosis had to be suspected in view of the symptoms and an elevated β-hCG. A Thyroid function test confirmed the same with elevated T3, T4 and decreased TSH. USG of the neck did not reveal any nodules/enlargement.

Patient was initially started on anti-thyroid drugs (Carbimazole) to control his symptoms. After consultation with Medical Onchology, a chemotherapeutic regimen was started with BEP regimen(Bleomycin,Etoposide, Cisplatin) which showed initial decrease in β-hCG. This was continued for 6 weeks. Unfortunately, patient developed liver cell failure and succumbed to the disease 2 months after the initial diagnosis.

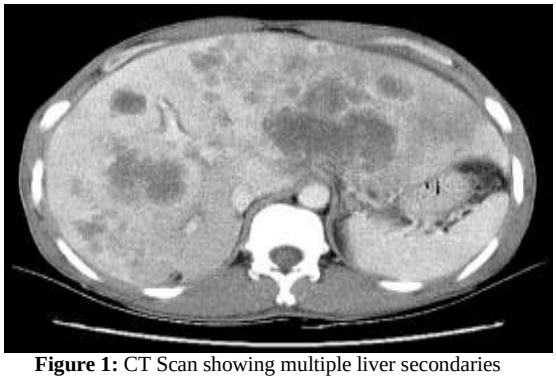

Figure 1: CT Scan showing multiple liver secondaries

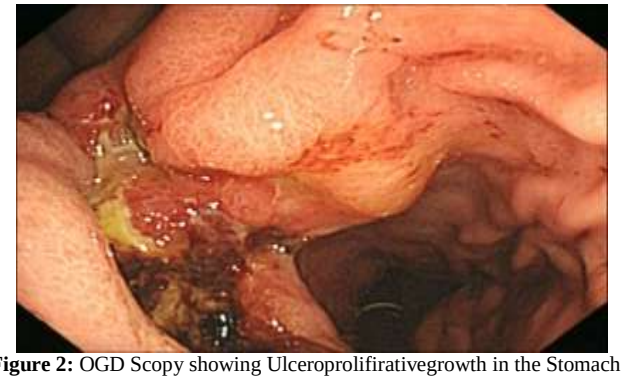

Figure 2: OGD Scopy showing Ulceroprolifirativegrowth in the Stomach

III. Conclusion

A metastatic choriocarcinoma from a primary gastric cancer presenting with overt hyperthyroidism, is an extremely rare presentation. To avoid misdiagnosis, all cases should be carefully evaluated, not only to identify the nature of primary tumor, but to also recognize this rare, yet life threatening paraneoplastic presentation of hyperthyroidism.

IV. Discussion

Choriocarcinoma is a germ cell tumor including syncytio-trophoblastic cells, and it secretes β-hCG. In female cases, it occurs as the pregnancy choriocarcinoma pattern, non-pregnancy choriocarcinoma occurs frequently in the mediastinum, ovary, etc., and in male cases, it occurs in the testis although rare. Extragonadalnongestationalchoriocarcinoma is developed rarely in the mediastinum, retroperitonium, pineal gland, liver, gallbladder, urinary tract system, etc., and the development in the stomach as primary has been known to be very rare. Until now, most cases are reported as the case report style, and the situation is that the development mechanism of disease, prognostic factors and treatment modalities are hardly known.

A. Clinical Characterstics

Noguchi et al. collected 19 cases and reported, and Kobayashi et al. analyzed 53 cases of primary gastric choriocarcinoam retrospectively and reported[1-3]. In Korea, primary gastric choriocarcinoma (PGC) was reported in 1975 for the first time, and until now, total 8 cases have been reported[4].

In the present case, the patient is a 62 yr old Male, with presenting complaints of Upper abdominal pain. No surgery was done. Chemotherapy was initiated with BEP regimen and patient expired after first cycle.

According to Kobayashi et al., the mean age of the onset of PGC in the male is 62.4 years, the female is 54.8 years, the ratio of the male and the female was 2.3:1, and as the development site, it was developed most frequently in the lower 1/3 of the stomach This is the result concurring to the preferential area developing gastric adenocarcinoma. In addition, tumor size was average 7 cm, and in endoscocpic results, hemorrhage or necrosis was accompanied in most cases. In histological findings, adenocarcinoma was accompanied in 70%, and at the time of surgery, most patients had metastasis. As metastasis area, lymph nodes were most common (87%) followed by the order of the liver (45%), peritoneum (23%), and lung (8%)[5].

B. Mechanism Of The Development Of PGC

As the mechanism of the development of PGC, several hypotheses have been proposed. First, the hypothesis that it is developed from putative displaced gonadal anlage , Second, by the delayed metastasis of unidentified primary lesion in the uterus , third, the hypothesis of the retrodifferentiation of gastric adenocarcinoma tissues[6], and fourth, the hypothesis that it is developed from teratoma[7]. Among them, although it is still largely controversial, generally, the retrodifferentiation theory from gastric adenocarcinoma suggested by Pick has been accepted[7]. This is that malignant gastric adenocarcinoma tissues retrodifferentiate to the embryonal ectoderm level and acquire the ability to produce trophoblasts, and Liu et al. have reported that PGC has the genetic characteristic of adenocarcinoma and pregnancy choriocarcinoma[1]. Proofs supporting the retrodifferentiation theory are that 71% of primary choriocarcinoam is associated with adenocarcinoma, the mean onset age of these primary choriocarcinoma is 56 years, and it is comparable to the mean onset age of gastric adenocarcinoma, 62 years. On the other hand, choriocarcinoma occurred after pregnancy is developed in the female primarily. In addition, the point is that primary gastric choriocarcinoma was reported abundantly in the area where the incidence of gastric adenocarcinoma is high, particularly, Japan, etc .

In such manners, in PGC cases, choriocarcinoma and adenocarcinoma are present concurrently in many cases, and it was difficult to obtain sufficient specimen only by endoscopic biopsy, and thus it was diagnosed as adenocarcinoma in many cases. According to Kobayashi et al., cases diagnosed accurately by endoscopic biopsy was only 8%. Therefore, in endoscopic finding, for cases showing hemorrhage or necrotic big tumors, it is

important to obtain sufficient tissues during biopsy. Kobayashi et al. have observed that prognostic factors showing short survival period were the presence of liver metastasis simultaneously, systemic chemotherapy was not administered, etc., and particularly, in cases with concurrent liver metastasis, most patients died within one month. Therefore, the authors recommended not to perform conservative gastric resection for cases with liver metastasis concurrently[4].

C. Diagnosis Of PGC

Regarding the diagnosis of PGC, it is ideal to diagnose by performing clinical symptoms, the quantitative test of serum chorionic gonadotropin, radiological finding, and histological test in combination, nevertheless, as in our cases, in primary gastric case, it is not easy to differentiate from advanced gastric adenocarcinoma. Therefore, a method is to rule out other possible primary lesions, and after the resection of primary lesion, to confirm that β-hCG becomes normal. In male cases, the primary lesion may be in the testis, nevertheless, it may be fibrous or calcified, and thus comprehensive tests are required. Pathological definite diagnosis is prerequisite, and for the diagnosis, after the assessment of cytotrophoblast and syncytiotrophoblast, to confirm β-hCGpositve cells by immunohistochemical test, and to confirm the high elevation of β-hCG in the blood. In addition, to prove that the stomach is the primary site, the absence of choriocarcinoma in the ovary, testis and retroperitoneum should be proven.

D. Treatment Of PGC

For the treatment of gastric choriocarcinoma, chemotherapy engaging methotrexate, actinomycin D, etoposide, folinic acid, vincristin, cyclophosphoamide, etc. is the main therapy, and as supplement, surgery or radiation therapy is administered. For choriocarcinoma and adenocarcinoma, their chemotherapy modality is different, and thus for patients diagnosed to be adenocarcinoma showing elevated β-hCG, it is required to assess the concurrent presence of choriocarcinoma. As the treatment for gastrointestinal choriocarcinoma, due to the hemorrhagic characteristic of choriocarcinoma, hemorrhage is associated in most cases, and thus its treatment should be considered. For cases with liver metastasis, to prevent the death caused by hepatic hemorrhage, the ligation of hepatic artery or hepatic lobectomy may be considered. The mean survival time of patients with choriocarcinoma is less than 2 months and it is very poor. The survival rate could not be improved even by chemotherapy consisting of several chemotherapeutic agents, and radiation therapy also could not be of help to prognosis[8]. According to the study reported by Kawashima et al., hepatic failure caused by liver metastasis was common cause of death, and cancerous hemorrhage was the next common cause of death. In addition, other causes of death were DIC, dyspnea, etc.

E. Metastatic ChoriocarcimomaAnd Hyperthyroidism

Human chorionic gonadotropin may result in hyperthyroidism through crossreaction with the TSH receptor. There is a partial correlation between hCG concentration and the severity of the hyperthyroid metabolic state (25,000U/L of hCG are roughly equivalent to 1mU/L of TSH activity). Most commonly, the hCG-induced alteration of thyroid function results in suppression of TSH and elevation of free T4.

Symptomatic hyperthyroidism can be treated with beta receptor antagonists and/or anti-thyroid drugs. Cure of the tumor will result in treatment of the hyperthyroid state.

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