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A Late Gastric Adenocarcinoma Recurrence with Bone Marrow Infiltration: Presentation of an Interesting Case

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Gastric cancer; Adenocarcinoma; Chemotherapy; Bone marrow infiltration; Prognosis

1. Abstract

Gastric cancer is a global health problem and usually is related with poor prognosis. Herein, we present a 71-year old patient case who initially diagnosed with a locally advanced, grade III, signet ring, gastric adenocarcinoma. An operation was initially performed and systemic chemotherapy was administrated afterwards. Despite the initial advanced stage, poor clinical and pathology prognostic factors the patient had a long disease free period. Unfortunately,7 years later he was diagnosed with local recurrence and bone marrow infiltration. He had again an unexpected excellent response to therapy with a survival of 16 months. Nowadays, personalized medicine is considered to be the ideal approach in order to offer effective treatment. Clarifying the pathways and the pathophysiologic mechanisms through molecular biology, is the key to tailor our patients' therapy and have optimal results.

2. Introduction

Gastric cancer is a major worldwide health problem. It is the third leading cause of death attributed to malignancy and more than a million people are expected to be diagnosed globally. The incidence is higher in Eastern Asia, while in contrast countries of North Europe and North America maintain a relatively low rate [1].

Despite recent advances in cancer therapeutics, the survival of locally advanced or metastatic disease is dismal. It is evident that a wide spectrum of prognostic and predictive biomarkers is needed in order to rationalize our decisions and tailor their therapy. Furthermore, there is no doubt that the therapeutic algorithm should be always decided and planned by multidisciplinary groups.

3. Case Report

A 71-year-old man with a history of epigastric pain and loss of 10 kg the last 3 months was initially evaluated by his family doctor. Despite being treated symptomatically, his symptoms persisted and a thorough investigation with laboratory tests and an upper gastrointestinal endoscopy revealed an ulcerated mass in the pyloric antrum. The biopsy confirmed the diagnosis of malignancy (grade III, adenocarcinoma, diffuse type, signet ring). The computerized tomography (CT) scans of the chest, abdomen and pelvis showed thickening of the pyloric wall as well as a few pulmonary suspicious nodules requiring monitoring. Unfortunately, he was not evaluated by a multidisciplinary team meeting (MDT) and subsequently a partial gastrectomy and Billroth II anastomosis was performed (19/05/2011). The pathology report showed a diffuse-type gastric adenocarcinoma with infiltration of the duodenum and TNM staging pT3N3b (23+/23), grade III, with possible infiltration of the surgical site (R1?).

He was assessed for the first time at Bank of Cyprus Oncology Center (B.O.C.O.C.) after the operation. After the evaluation of the patient's data during the gastrointestinal cancer MDT of our centre, it

was decided that he should receive systematic therapy with the EOX combination (ebirubicin, oxaliplatin, capecitabine). The stage was considered as advanced and probably early metastatic. The patient received in total 6 chemotherapy cycles of EOX (27/6-28/10/2011) and then he was set in follow up. Further investigation showed HER-2: 0 (IHC), MSS (microsatellite instability stable, RT-PCR). Re-staging with CT of the chest, abdomen and pelvis following the completion of chemotherapy didn't reveal metastatic lesions and the upper GI endoscopy confirmed no active disease.

During the following years the patient was in a follow-up schedule according to the guidelines, without any evidence showing relapse of the disease.

Unfortunately, in February 2018 the patient presented with melaena stools and a significant fall in hemoglobin (Hgb=7gr/dl) due to which he was admitted in the local General Hospital. Investigation through gastroscopy showed a large thrombus in the cardioesophageal junction area and signs of malignancy, confirmed by a biopsy. A CT of the chest-abdomen-pelvis and an MRI of the spine where then performed and revealed wall thickening of the gastroesophageal junction as well as multiple secondary bone lesions (Figure 1, 2). During hospitalization, derangement of the coagulation markers was noticed with prolongation of PT and PTT, a fall in fibrinogen levels, thrombocytopenia and schistocytes in the peripheral blood smear from which the diagnosis of disseminated intravascular coagulation (DIC) was established. More specifically laboratory results were as followed: INR 1,4, PT: 7,4sec, PTT: 26,1sec, D-dimers 6,739μg/L, fibrinogen 119mg/dl, hemoglobin: 7,3g/dl, PLT: $77*10^9$ /L, CEA< 3u/ml, CA 19-9: 4,107 U/ml, LDH: 678 U/L, Bilirubin: 1,24 mg/dl. Multiple transfusions with red blood cells and fresh frozen plasma were needed until the patient was stabilized. Due to multiple bone metastasis and the clinical diagnosis of DIC, the suspicion of bone marrow infiltration was set which was established after a bone marrow biopsy (Figure 3, 4). It was then decided to offer palliative chemotherapy. He received 8 cycles of FOLFOX (40% dose reduction-oxaliplatin, folic acid, fluorouracil: 26/03-07/07/2018). Following this, he was given 5 cycles of single agent with capecitabine tablets (1000mg, bd, day 1-14, 21 days' cycle, 18/8-18/12/2018). The patient's response was excellent and as a consequence, after the second cycle of chemotherapy, there was no need for further support with transfusions (RBC, FFP) while the tumor marker CA 19-9 dropped in normal levels (19/07/2018= 14U/ml).

Unfortunately, clinical deterioration was noted once again in April 2019, almost 13 months after disease recurrence, while the tumor marker CA 19-9 was elevated above >10000 U/ml. During the same period, hospitalization was needed because of laboratory findings indicative of severe DIC. Daily transfusions with red blood cells and fresh frozen plasma were given while a challenge chemotherapy with 5FU (2 cycles) was attempted. Further investigation of PD-L1 expression turned out negative (CPS<1). Since then, the patient presented with further clinical and laboratory deterioration, impaired kidney function, severe episodes of infection, episodes of pulmonary edema and as a result chemotherapy was discontinued. After all, the patient passed away in 05/06/2019 while being hospitalized.

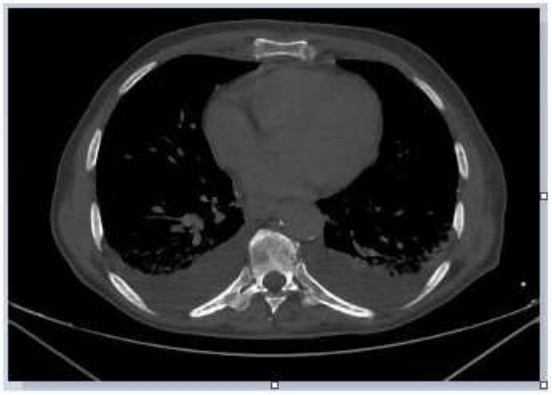

Figure 1a: CT scan images. Diffuse-multifocal osteolytic, ill-defined lesions of variable size affecting the hole skeleton: a. axial section at the thoracic level.

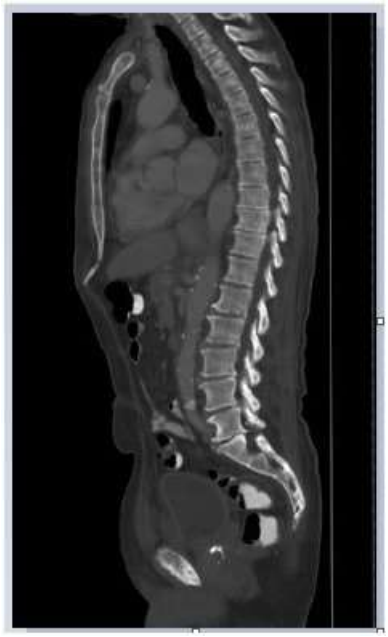

Figure 1b: sagittal reconstruction of the spine.

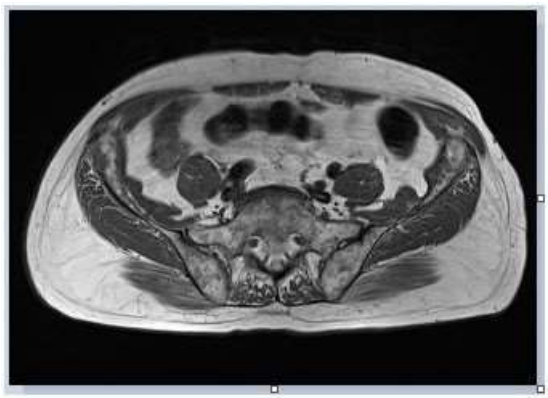

Figure 2a: MR T1 Images. Diffuse-multifocal replacement of the normal bone marrow signal intensity of examined parts of the skeleton (sacrum, pelvic bones): a. axial section at the level of the pelvis,

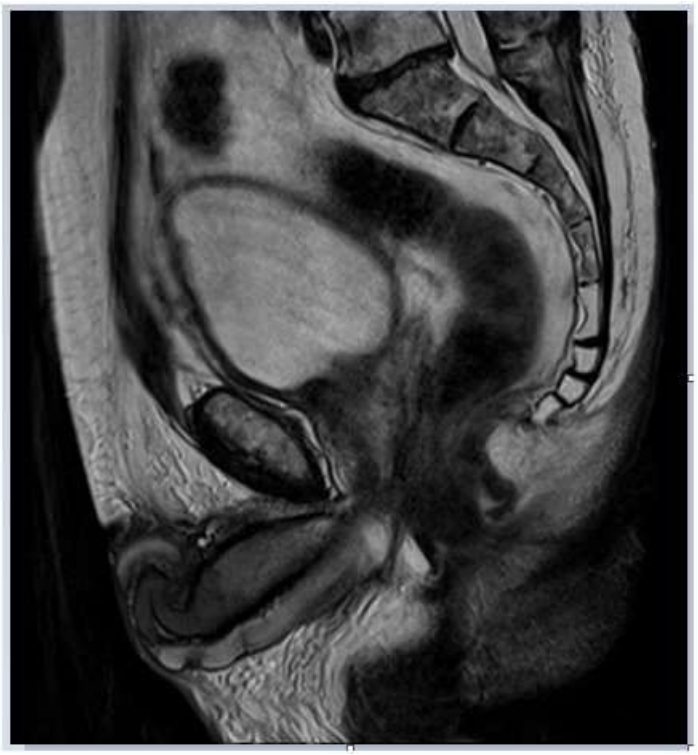

Figure 2b: sagittal view at the same level.

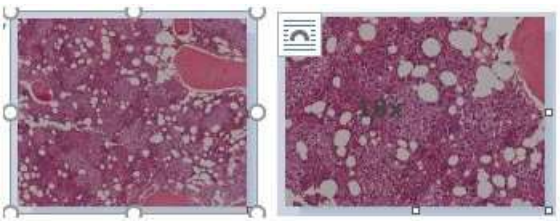

Figure 3(a, b): The bone marrow shows extensive metastatic infiltration by a high-grade carcinoma with a diffuse growth pattern (a, b).

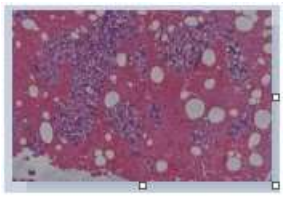

Figure 3c: It consists of cells with a signet ring morphology that contain mucus in their cytoplasm. Histochemical staining of Alcian blue reveals intracellular mucus (c).

Figure 4: Tumor cells are positive for keratins AE1 / AE3 (a) and CK7 (b) and negative for keratin CK20 (c).

4. Discussion

In this article we present an interesting case with an exceptional response, despite the initially advanced stage (p T3N3, R1? suspicious tiny lung lesions) and poor prognostic factors (diffuse type adenocarcinoma, signet ring cells, HER-2:-, MSS). There lapse occurred almost 7 years after the initial diagnosis. Even after the diffuse relapse with multiple bone metastasis and bone marrow infiltration with the prognosis being poor, the patient's response was once more unexpected.

This group of patients have ominous prognosis, with an estimated survival of less than 6 months from diagnosis and rarely reaching one year. There are data from studies related to different types of malignancies where systemic chemotherapy seems to be beneficial [2, 3]. The majority of patients pass away due to disease progression, but the causative factor could be an infection or a DIC manifestation such as cerebral hemorrhage.

It is worth to be noted that the patient was initially treated by the EOX regimen which was the optimal therapeutic choice at that time period his cancer was diagnosed. Following that, several studies (UK-MRC OE05, FLOT trial) showed no benefit from the administration of anthracic lines which are currently not the optimal treatment approach anymore [4, 5].

Nowadays, personalized medicine is considered to be the ideal approach in order to achieve the optimal results in several diseases. Clarifying the pathways and the pathophysiologic mechanisms through molecular biology, is the key to offer the optimal treatment. However, there are still a lot to study and understand. Why patients sharing common characteristics present different outcomes? Why patients whose prognosis is initially bad, end up with excellent outcomes or vice versa? What is the exact role of tumor heterogeneity, tumor intrinsic factors and immune microenvironment? All the above are the questions remaining to be answered. The answers, if any, need to be incorporated in our daily clinical practice and armamentarium in order to achieve the best outcomes for our patients.

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