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CASE REPORT

Uncommon Initial Presentation of Gastric Cancer with Bone Metastases: a Case Report

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Introduction

Gastric cancer (GC) occupies the second leading cause of death worldwide with 600,000 deaths per year [1, 2]. In Mexico, it occupies the fifth cause of death, with 6 751 deceased per year; this situation is rising due to the high prevalence of chronic degenerative disease, aging, and population growth. However, the extraordinary efforts of prevention and early diagnosis have fallen greatly over the past decades [1, 3, 4]. One third of patients have locally advanced disease and metastatic illness at the time of the diagnosis [3, 5]. GC is asymptomatic in early stages, the clinical features are unclear and varied, clinical alarm data (unexplained weight loss, patient age > 55 years, early postprandial fullness or upper gastrointestinal bleeding) are present in advanced stages [6, 7]. The metastases of GC are by local extension through the lymphatic system of the stomach wall. The locations most frequently observed in metastatic disease are liver 54%, lung 22%, pancreas 19%, adrenal gland 15%, and bone < 10% [5, 8]. Bone metastases (BM) are an uncommon event in patients with advance-stage GC and are rarely an initial presentation [8]. The most common affected sites by BM are spine, ribs, scapula, and pelvis; the clinical features of BM are unspecified, and BM may present unexplained lumbar pain with poor medical response, pathological fractures, and spinal syndromes [9, 10]. The case presented exemplifies the difficulties faced at diagnosing GC with atypical manifestations.

Case Report

A 47-year-old man was brought to the emergency department, documenting generalized weakness and low backache with gradually increasing pain (9/10 of AVS [Analogous Verbal Scale]) impairing ambulation. Past medical history highlights weight loss of approximately 20 lbs and early postprandial fullness since 2 months ago. He had an eight-year history of diabetes mellitus type II without treatment; he denied smoking, alcohol, and drug abuse. There was no family history of gastrointestinal-associated neoplasia.

During clinical assessment, the patient denied history of lumbar trauma, lower extremity numbness, and fecal or urinary incontinence, on exploration reflexes in both extremities were normal. His laboratory tests were abnormal as follows: alkaline phosphatase, 450 IU/L; lactic dehydrogenase, 584 IU/L; carcinoembryonic antigen, 34 ng/mL; and alpha fetoprotein, 96 ng/mL. Other laboratory studies, such as serum electrolytes, total proteins, nitrogenous elements, and prostate-specific antigen were found normal. In addition, the initial radiograph showed several osteolytic lesions in the low thoracic and lumbar region (T11–L4) and fragmentalization of the T12 vertebral body. Next in order, we performed CCT scan, finding abnormal thickening of the stomach wall, retroperitoneal, and loco-regional lymphadenopathy, in addition to lesions in the low thoracic and lumbar region, with neither hepatic nor kidney observable metastases (Fig. 1). The initial suspicion was malignancy considering the fast and

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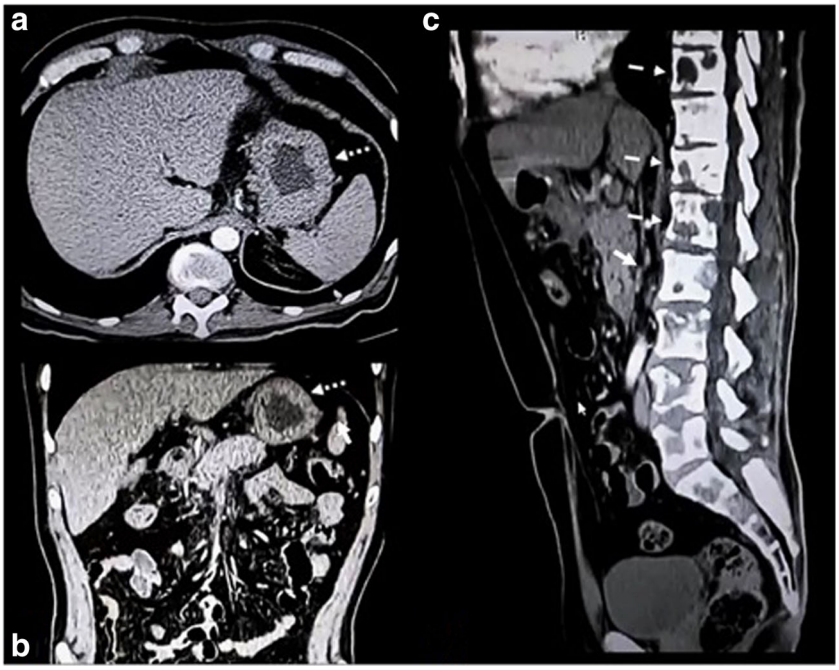

Fig. 1 CT scan contrasted. a), b) The abnormal thickening of the stomach wall (dotted arrow) and loco-regional lymphadenopathy (full arrow). c) Exposed osteolytic lesions in vertebral column (cut arrow) and retroperitonea lymphadenopathy (full arrow)

unexplained weight loss, early postprandial fullness and patient's age. However, it was necessary to rule out multiple myeloma (MM), due to the high frequency of affecting the axial skeleton. We performed transpedicular vertebral body biopsy a week later the endoscopy was performed: the esophagus of normal aspect, normal-looking stomach in its cardiac and fundal portion, intense diffuse erythema was observed in the first portion of the stomach, while in the greater curvature was observed normal. The antral region was diffuse erythematous in appearance and the pylorus was normal and easily canalized. Two biopsies of the erythematous zones and two marginal tissue biopsies were taken by means of standard endoscopic clamp without stylet. The endoscopic procedure had no complications or recovery after anesthesia. The histopathological report of bone and gastric biopsies were positive for SRCGC (Fig. 2). Therefore, differential diagnoses were excluded (MM, prostatic cancer, and spinal tuberculosis) (Fig. 3).

Subsequently, we started treatment with palliative chemotherapy based on 5-fluorouracil 800 mg/m^2/day, cisplatin 30 mg/m^2/day, and epirubicin 50 mg/m^2/day, as well as ondansetron and dexamethasone in constant infusion to control vomiting and nausea. The patient showed constant worsening and deterioration of his clinical condition after his first cycle of chemotherapy with incoercible vomiting and hepatic encephalopathy. Unfortunately, the patient died secondary to upper gastrointestinal bleeding probably due to Mallory-Weiss syndrome; however, endoscopy was not performed due to the hemodynamic instability of patient.

Discussion

BM are common in lymphoma, prostate, breast, lung, kidney, bladder, thyroid, and sarcoma carcinomas, which can be osteolytic, osteoblastic, or both [11]. However, it is known that 33.3–50% of GC are asymptomatic and present initially with distant metastasis, but infrequently to bone. The reported incidence of metastasis to bone as an initial presentation of GC is 1–8% in clinical practice; this data is affected due to the

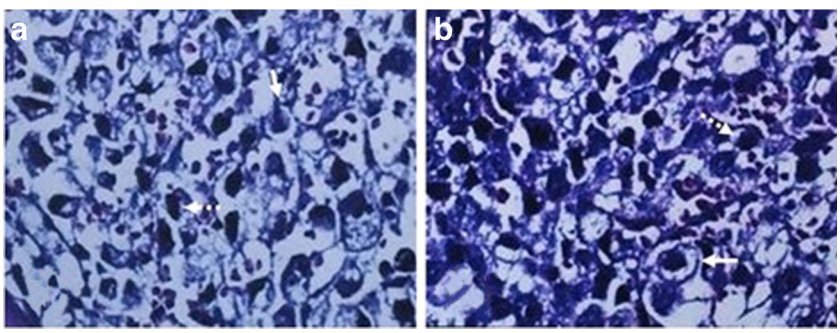

Fig. 2 Histopathologic bone biopsy (lumbar vertebrae). a), b) Hyperchromatic nuclei and loss of nucleus cytoplasm ratio (dotted arrow), in addition cell with typical characteristics in signet ring (full arrow)

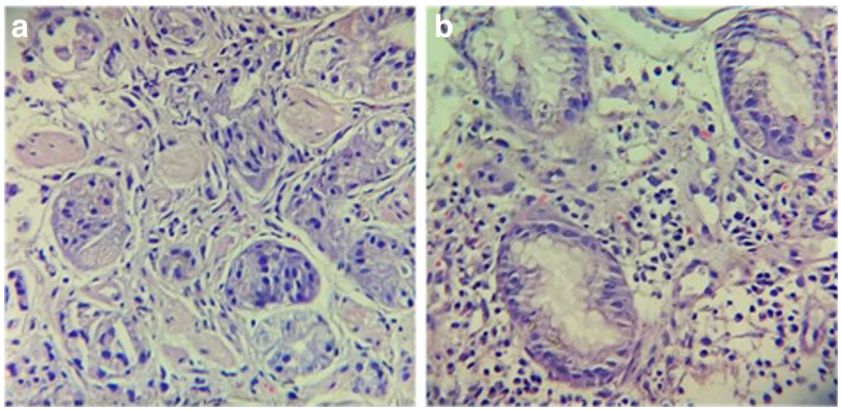

Fig. 3 Body gastric biopsy showed cellular atypia and pleomorphic cells infiltrated in all the thickness of the gastric wall characterized by signet ring cell gastric carcinoma

majority of asymptomatic cases and the diagnosis of GC already established [3, 5, 12, 13]. There are no defined risk factors for developing BM, although, associations can be established. In a hospital of the Republic of Korea, an observation was made in patients with GC and BM, in which they report that there are independent predictors for initial BM, which were early age, signet ring cell histology, primary tumor involving two thirds of the stomach, pleural metastasis, thrombocytopenia, and elevated alkaline phosphatase, in similitude to our findings which were 47-year-old man, great thickening of the stomach wall, histology reported SRCGC, as well as an elevated level of alkaline phospatase [14]. Concluding, an early age and elevated alkaline phosphatase may be good clinical markers to make us suspect bone metastases in these clinical scenarios as well as including SRCGC biopsy results.

Gastrointestinal symptoms in GC with initial BM have been infrequently documented; in a multicenter study, it was reported that only 3% of GC had initial BM, but BM percentage without involvement of other organs is unknown [1, 15]. Even so, the predominant symptom is weight loss; this complicates the diagnosis and opens up to a wide range of differentials.

The dissemination to the bone is usually by the lymphatic vessels and veins [12, 16]. The sites most affected by BM are spine, ribs, scapula, pelvis, and axial skeleton in 20%; the clinical characteristics are not specific and they may present with refractory pain, pathological fractures, hypercalcemia, and spinal syndromes [1, 17]. The patients clinical features at arrival to the hospital were refractory lumbar pain and weight loss, on physical examination no abnormalities were found.

Laboratory studies may suggest the possibility of malignancy and BM, for example: anemia, alkaline phosphatase, lactic dehydrogenase, carcinoembryonic antigen, and alpha fetoprotein play an important role in patients with occult adenocarcinomas. GC cells can also produce alpha fetoprotein and represent blood-borne metastases from tumor cells or solid organ tumor involvement, as well as frequent hepatic metastases in patients with BM [18]. Therefore, topographic extension studies are required, such as computed tomography contrast with portal phase for optimal detection of liver metastases, positron emission tomography aiding topographical and lymphatic extension, and bone scan as a study of choice for detecting BM [19, 20]. We must not forget that the initial method of noninvasive imaging for GC and BM is computed tomography; this of course must be accompanied by the necessary extension studies and tumor markers to guide the diagnosis. In some special cases, invasive diagnostic methods may be required, such as a laparoscopic approach, also useful in establishing resectability and directing treatment with a sensitivity of 88% and specificity of 100% [21]. BM may occur more frequently in diffuse-type GC, especially in SRCG [8, 16]; the characteristics include poorly differentiated histology, vessel, and perineural invasion, CDH1 gene mutation (1–3%), sporadic loss of the p53 allele (60%), and epidermal growth factor receptor (EGFR) expression. Vascular endothelial growth factor (VEGFR) and human epidermal growth factor receptor 2 (HER2-neu) are related to worse prognosis than other types of GC [5–8, 22, 23]. We followed a protocol of refractory low back pain, which by age and due to few clinical data lead us to an extensive search of the etiology, ruling out multiple myeloma, the different locations of primary tumors that metastasize to bone, and primary tumors of the bone, among others. The biopsy obtained showed a classic histological strain reported in this type of metastasis, unfortunately, we could not perform a genetic study. However, it is remarkable that bone metastases was found and analyzed, which has been reported very little around the world.

Regarding management, patients in terminal stage are treated with palliative chemotherapy based on a fluoropyrimidine/cisplatin regimen, improving survival, reducing the risk of death by 61% compared to surveillance and supportive care [23–25]. It is recommended to examine HER-2 status and to add trastuzumab to the standard pattern in positive tumors [25, 26]. Regarding the treatment of clinical manifestations of BM, the use of radiotherapy is recommended, some authors recommend metrotexate combined with the chemotherapy regimen,

thus achieving a combination of agents with dual biochemical modulation therapy [27].

In general, overall survival is 3 to 4 months without treatment and 8 to 11 with chemotherapy [7, 14, 28]. The patient underwent the first cycle of chemotherapy as recommended in different articles and in guides that govern our country. However, the outcome was fatal, leading to death in a few weeks.

Little is known about the issue, however, GC's incidence has increased as well as its unexpected or initial manifestations, it is recommended to take into account even the most minimal symptoms to make a quick and accurate diagnosis. Establishing the fact that patients with BM have a worse outcome than even those with multiple metastasis. In this case, we highlight the importance of an accurate and early BM diagnosis, as well as a more informative approach to diagnosis GC patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human Rights Statement and Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This study was performed with nationwide, anonymous data; thus, informed consent or substitute for it was waived by the ethical review board of the Hospital General de Morelia.

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