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Case Report

Denovo Metastatic Primary Gastric Ewing Sarcoma/Primitive Neuroectodermal Tumor– 13 Years Follow-up: Case Report and Review of Literature

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ABSTRACT

Ewing sarcoma/primitive neuroectodermal tumors (ES/PNETs) are small round cell malignancies that originate mostly from the skeleton and less frequently from extrasketal tissues. Primary gastric ES/PNET is a very rare entity. In August 2011, a 19-year-old male patient was admitted to our hospital with complaints fatigue, weight loss and black stools. Gastroscopy revealed a 10cm diameter malignant necrotic, hemorrhagic, ulcerated mass lesion in the gastric corpus. Biopsy showed small round malignant cells staining positive for CD99. Fluorescence in situ hybridisation (FISH) demonstrated t(11;22)(q24;q12).. PET/CT showed a lesion compatible with primary malignancy in the stomach and metastatic lesions in the liver. VAC-IE protocol was administered with the diagnosis of Primary Gastric ES/PNET and complete remission in the liver and significant regression in the stomach was achieved. Gastric wedge resection was performed and adjuvant chemotherapy was completed. The patient has been followed up and has been in remission for 12 years since the first chemotherapy.

1. Introduction

Ewing's sarcoma/primitive neuroectodermal tumor (ES/PNET) family are small, round cell, high-grade malignant tumors of neuroectodermal origin, arising from bone or extraskeletal soft tissue[1]. Extraskeletal Ewing's sarcomas (ESS), one of the members of the ES/PNET family, are rare malignancies with poor prognosis[2]. Ewing's sarcoma of bone (ESB) frequently arises from the long bones of the extremities and the flat bones of the pelvis, whereas ESS may arise from the extremities, retroperitoneum and head and neck region[3]. Primary gastric ESs have been reported very few times in the literatüre and there is no definite consensus on the treatment regimen since they are very rare[4,5].

Here, we present a case of primary gastric ES/PNET with liver metastasis at the time of diagnosis, which may help clinicians especially in the choice of treatment.

2. Case Report

A 19-year-old male patient was admitted to our hospital with complaints of weakness, fatigue, abdominal pain, nausea, anorexia, weight loss and black colored stools, in August 2011. For 6 months he had complaints of increasing malaise, fatigue, abdominal pain, nausea and loss of appetite. He had lost 12 kilograms in 3 months. He had black colored stools for the last 3 days. In his family history, his uncle was diagnosed with pancreatic cancer and his grandfather was diagnosed with laryngeal cancer.

On physical examination, the patient appeared pale. Abdominal examination revealed tenderness in the upper quadrants. Rectal examination was melena.

Blood pressure 85/60 mmHg pulse: 120 beats/min fever: 37.2 C. Laboratory examination revealed White Blood Cells: 9300/µL Neutrophlis: 8100/µL Platalets: 451000/µL hemoglobin:3.8g/dl, hematocrit:10.5 (%) C-Reactive Protein (CRP): 31mg/dl (n:0-5), renal and liver function tests were within normal range.

Treatment was organized with a prediagnosis of Gastrointestinal Hemorrhagia and 3 units of erythrocyte suspension was planned. The patient whose vital signs stabilized underwent gastroscopy. Gastroscopy revealed a 10 cm deep infiltrating, necrotic, hemorrhagic, ulcerated mass lesion in the gastric corpus. Multiple biopsies were taken.

Biopsy microscopy revealed small round malignant tumor cells. CD117 was strongly positive, CD99, vimentin and NSE were positive. CD3-CD20-CD34-CD45-CD56, S100, WT, Chromogranin A- Synaptophysin were negative. Ki67 index was found to be 70%. Fluorescence in situ hybridisation (FISH) demonstrated t(11;22)(q24;q12).

PET/CT showed a mass lesion measuring 119 mm in size in the antrum including the gastric corpus, pancreatic tail section, spleen, perihepatic areas and surrounding mesenteric areas with diffuse nodular hypermetabolic density increases and lymphatic invasion. Hypermetabolic metastatic mass lesions were seen in liver segments 5-6-7-8 **(Figure-1).**

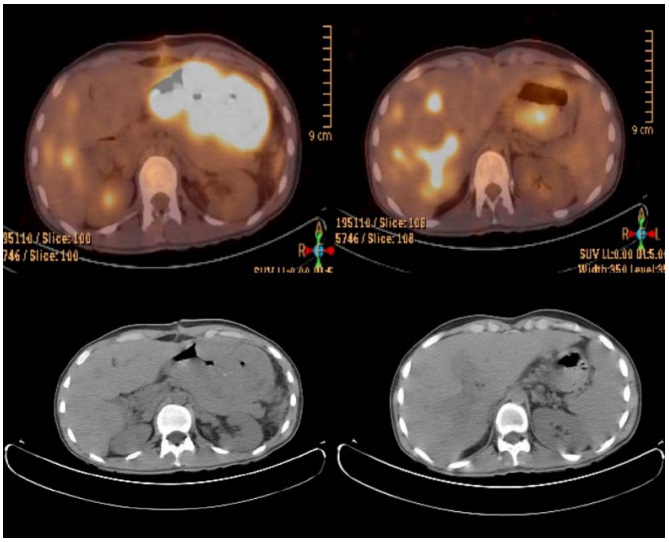

Figure 1: Before neoadjuvant chemotherapy.

1. stomach at the time of diagnosis on pet/ct
2. liver at the time of diagnosis on pet/ct
3. stomach at the time of diagnosis on ct
4. liver at the time of diagnosis on ct

In October 2011, with the diagnosis of metastatic primary gastric ES/PNET, vincristine 1.5 mg/m² (maximum dose 2mg/m2, doxorubicin 75 mg/m², cyclophosphamide 1200 mg/m² (VAC) on Day 1 alternating with etoposide 100 mg/m², ifosfamide 1800 mg/m² and mesna 1800 mg/m² (IE) daily for 5 days. After 3 cycles of VAC and 3 cycles of IE treatment, PET/CT was planned. PET/CT: liver complete regression, stomach marked regression was detected **(Figure-2).** After 6 cycles of VAC and 6 cycles of IE, the radiologic response persisted and gastric surgery was performed in June 2012. No viable tumor cell was detected in the pathology of the patient who underwent gastric wedge resection, but fibrosis and edema secondary to treatment were detected. The patient received 6 cycles of doxorubicin with a cumulative dose of 450mg/m2. Actinomycin D (1.25 mg/m²) was added instead of doxorubicin and VAC-VDC/IE treatment was completed with 8+8 for 16 cycles.

The patient was in remission when last examined in November 2024.

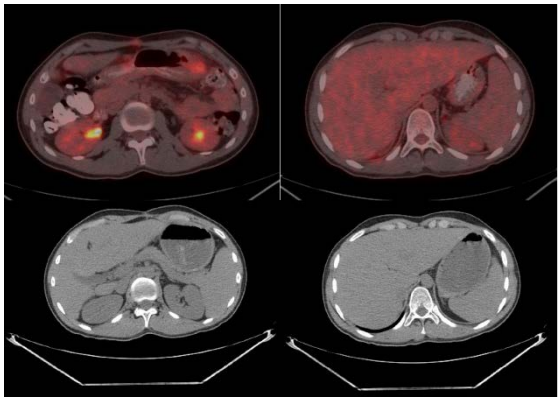

Figure 2: After neoadjuvant chemotherapy.

1. stomach on pet/ct
2. liver on pet/ct
3. stomach on ct
4. liver on ct

3. Discussion

The Ewing's sarcoma/primitive neuroectodermal tumor (ES/PNET) family includes Ewing's Sarcoma of bone (ESB), Extraskeletal Ewing's sarcomas (ESS), peripheral primitive neuroectodermal tumor (pPNET) and malignant small cell tumors of the chest wall (Askin tumor)[6]. The common feature of the ES/PNET family is the presence of CD99-staining small blue round cells and/or the EWS-FLI1 fusion gene formed by the t(11;22) (q24;q12) translocation[5]. Although CD99 is highly sensitive, its specificity is low[7]. Therefore, confirmation of the diagnosis by fluorescent in-sutu hybridization is recommended[5,8].

ESS/PNETs are extremely rare malignancies with an estimated incidence of 0.4 per million[9]. There are only 13 cases of gastric ES/PNETs reported in the literature so far[4,5,10-20]. We summarized these cases together with our patient in **Table 1**.

The ages of the patients, ranged from 14 to 66 years. 8 of 14 patients were female and 6 were male. Of the 14 cases, 4 involved the antrum and 10 involved the corpus. Tumor size ranged between 5 cm and 12 cm. 5 patients were metastatic (3 of them to the liver) and 9 patients were non-metastatic.

In the past years, ESS/PNETs were treated like soft tissue sarcomas[21]. However, it is now recommended that ESS/PNETs should be treated with the same chemotherapy approaches as all ES/PNET family members[22,23]. Under the same treatments, ESSs are known to give superior results compared to ESB[24].

There is no generally accepted treatment approach recommended for gastric ESS/PNETs. When we look at the cases of Gastric ESS/PNETs in the literature, it is seen that they are all treated differently. (see: **Table 1**).

Table 1: Clinical and pathologic characteristics and outcomes in

reported cases of gastric ES/PNETs.

Reference	Sex, age (years)	Location	Tumor size (cm)	Distant metastasis	Neoadjuvant chemotherapy	Surgery	Postoperative chemotherapy	Follow-up (months)	Outcome
Czekalla et al. (2004)	M, 14	Anterior wall body	7x3,5	Liver	VIDE	SG	Imatinib	24	AWD
Soulard et al. (2005)	F, 66	Antrum	8x5	No	No	Gastrectomy	Yes / Protocol NA	10	DOD
Rafailidis et al. (2009)	M, 68	Body	12	Liver*	No	SG	H/E and H/CDDP	13	DOD
Colovic et al. (2009)	F, 44	Posterior wall body	6,6x4,6	No	No	Excision	No	20	NED
Inoue et al. (2011)	F, 41	Anterior wall body	9x5,5	Peritoneal Metastasis **	No	DG	AC-İE	110	DOD
Kim et al. (2012)	F, 35	Antrum	5,5x2,5	No	No	WR	No	11	NED
Kumar et al. (2016)	F, 32	Lesser curvature body	11x6,5	No	No	Excision	VEC	12	NED
Song et al. (2016)	M, 55	High body	6,5	No	No	TG	Yes / Protocol NA	13	NED
Khuri et al. (2016)	F, 31	Lesser curvature body	11	Pancreas Splenic hilum	No	TDPSLA	No	36	NED
Maxwell et al. (2016)	F, 66	Antrum	11	No	No	DG	Dbc***	NA	NA
Hopp and Nguyen (2019)	M, 24	Posterior wall body	10x9	No	VAC-İE	DG	NA	NA	NA
Ye et al (2021)	M, 55	Posterior wall body	9x8	No	No	DG+ Roux-en-Y	No	8	NED
Shu et al (2023)	F, 19	Antrum	8,5x5	No	No	DG	VAC+İE	11	AWD
Our Case	**M, 19**	**Body and Antrum**	**10x8**	**Liver**	**VAC-İE**	**WR**	**VAC+İE**	**145**	**NED**

* 6 months later **6 years later ***only 1 cure

Abbreviations: NA: Not available; CG: Curative gastrectomy; DG: Distal gastrectomy; DG + Roux-en-Y: Distal gastrectomy + Roux-en-Y gastrojejunostomy; SG: Subtotal gastrectomy; TG: Total gastrectomy; TDPSLA: Total gastrectomy + distal pancreatectomy + splenectomy + left adrenalectomy; WR: Wedge resection; AWD: alive with disease; DOD: died of disease; NED: no evidence of disease; VEC: epirubicin, cyclophosphamide and vincristine; AC-İE :ifosfamide, etoposide, doxorubicin and cyclophosphamide; Dbc: doxorubicin based chemotherapy; VIDE: vincristine, etopposide, doxorubicin and ifosfamide; H/E and H/CDDP: Holoxan/epirubicin and Holoxan/CDDP(cisplatin).

Czekalla et al. had a patient with liver metastases who underwent subtotal gastrectomy after neoadjuvant vincristine, etoposide, doxorubicin and ifosfamide treatment. Afterwards, imatinib was initiated in the patient with expression of CD117 (c-kit) and the patient was followed up for 24 months without progression[10]. We, on the other hand, gave 2 more cycles of adjuvant chemotherapy to our patient who was strongly positive for CD117 without starting imatinib.

In 3 cases in the literature, only surgical procedures were performed. Neoadjuvant and adjuvant CT or RT were not administered. These patients were followed up for 11-20-36 months without progression[4,15,18].

Other cases were operated without neoadjuvant treatment and then different adjuvant chemotherapy protocols were applied[5,11-14,16-17,19].

Hop et al. applied neoadjuvant VAC-IE treatment in their cases and did not apply adjuvant treatment after surgery[20].

We applied 12 (6+6) cycles of neoadjuvant VAC-IE protocol to our patient who had denovo liver metastasis at the time of diagnosis and achieved complate remission in the liver and significant regression in the stomach. After gastric wedge resection, we applied 4 (2+2) cycles of VDC-IE protocol and followed up our patient. The patient has been in remission for 13 years since the first chemotherapy and 12 years since surgery.

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Conflicts of Interest

The authors declare no conflict of interest.

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