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CONTRACTING ORGANIZATION: University of California, San Diego, CA

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14. ABSTRACT

The project deals with identifying treatment and response targets for *Helicobacter*-associated gastric cancer. The purpose is to discover novel druggable targets by testing efficacy of approved compounds. An additional purpose is to identify immune related genes as predictors of treatment response. To accomplish the goals of our project we are using fresh gastric tumor tissue samples harvested from patients undergoing gastrectomy to generate patient-derived xenograft (PDX) and patient-derived orthotopic xenograft (PDOX) models. In addition, the work makes use of gastric cancer patient samples stored at our UCSD's Moores Cancer Center Biorepository core. We have successfully established a gastric cancer PDX model and show that tumor gastric tissues in the PDX model express the same genes as in the original tumor. In the first year we reported on expression of cancer markers such as the carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) and the tumor-associated glycoprotein 72 (TAG-72) in patient gastric tumors. These cancer markers were undetectable in normal gastric tissue. In the second year the significant finding was data showing a correlation between the expression level of a chemokine, C-X-C motif chemokine 5 (CXCL5) and the extent of malignancy. Figure 1 (below) shows CXCL5 expression levels in gastric cancer tumors. An accompanying summary of all patients and their gastric tumor characteristics are provided in Table 1 of an appended publication to this report.

15. SUBJECT TERMS					
Helicobacter pylori, gastric cancer, patient-derived xenograft (PDX), patient-derived orthotopic xenograft (PDOX), differentially expressed genes (DEGs).					
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TABLE OF CONTENTS

1. INTRODUCTION:

The project deals with the identification of treatment and response targets of *Helicobacter*-associated gastric cancer. This work leverages our findings from our mouse model of gastric cancer(1, 2) to discover novel druggable targets by testing efficacy of approved compounds and to identify predictors of treatment response using freshly obtained patient gastric tissue samples, patient-derived xenograft (PDX), and patient-derived orthotopic xenograft (PDOX) models. In addition, the work makes use of gastric cancer patient samples stored at the tissue biobank at the UCSD's Moores Cancer Center Biorepository core.

2. KEYWORDS:

Helicobacter pylori, gastric cancer, patient-derived xenograft (PDX), patient-derived orthotopic xenograft (PDOX), differentially expressed genes (DEGs).

3. ACCOMPLISHMENTS:

What were the major goals of the project?

3.1: The major goals of the project are to deliver drugs to slow or stop the progression of gastric cancer and to determine patients likely to respond well to a specified drug.

What was accomplished under these goals?

3.2:

Correlation of expression levels of a chemokine, C-X-C motif chemokine 5 (CXCL5) with extent of malignancy. We evaluated expression of select differentially expressed genes (DEGs) that were associated with aggressive disease in our mouse model of gastric cancer including tumor necrosis factor alpha (Tnfα), Cxcl9, Cxcl5, Cxcl10, Beta-2-microglobulin (B2m), cluster of differentiation (Cd74), and Cd247 for their capacity to predict treatment response. We examined the expression of these genes in 14 gastric cancer tumor tissues (T) obtained from the UCSD Cancer Center Biorepository and new presenting patients at our center. Total RNA was isolated from the patient gastric cancer tissue and processed for quantitative real-time polymerase chain reaction (qRT-PCR), as described in our previous studies (1, 3-5), using the Direct-zol RNA mini kit (Zymo Research Corp) according to the manufacturer's instructions. RNA quality was determined by using a Nanodrop system (Thermo Fisher Scientific, Inc., Waltham, MA, USA) followed by reverse transcription into cDNA using the High Capacity cDNA Reverse Transcription kit (Thermo Fisher Scientific, Inc.). The expression of genes for each sample was expressed relative to its glyceraldehyde-3-phosphate dehydrogenase (GAPDH) using comparative cycle threshold calculations (ΔC_T, Applied Biosystems) and plotted using GraphPad Prism software. A summary of all patients and their gastric tumor characteristics are provided in Table 1 of the appended publication. We observed that the expression levels of CXCL5 was linked to the extent of malignancy (Fig. 1). In particular, overexpression of CXCL5 was associated with genomically silent and refractory gastric tumors. Tumors from these patients were poorly differentiated and patients had a significantly lower survival rate compared to patients with tumors that had low CXCL5 expression levels. This work is published and is upended as part of the technical report.

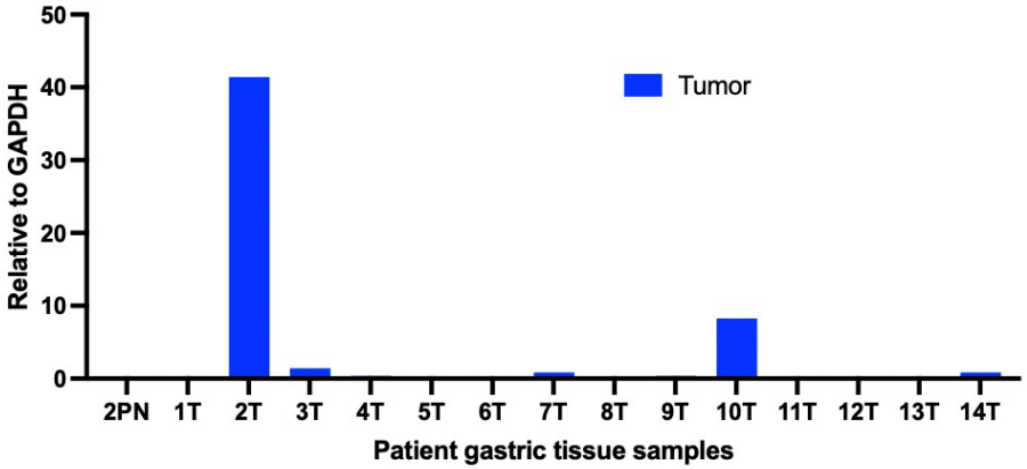

Figure 1. CXCL5 expression in gastric biopsies. CXCL5 expression was quantified by qRT-PCR and expressed relative to GAPDH using comparative cycle threshold calculations (ΔC_T, Applied Biosystems). 2PN, paired normal control of case patient (2T); T, tumor gastric cancer tissue.

Expression of target genes in patient-derived xenograft (PDX) and patient derived orthotopic xenograft (PDOX) models of gastric cancer. The PDX model was generated in the first year of the project as reported in our previous technical report. Figure 2 is an example of a successfully established gastric cancer PDOX model. This orthotopic or "same site" implantation of gastric cancer tumor will allow us to test efficacy of our select compounds that potentially prevent metastasis. We have analyzed gene expression of DEGs of interest in freshly obtained patient gastric tissue (original) and gastric tissue from the same patient implanted in nude mice (PDX and PDOX tumors) and did not observe significant differences in gene expression between the original tumors and PDX- or PDOX-generated ones. As expected, the COVID-19 pandemic affected the number of gastric cancer patient surgeries performed. While patient gastric surgeries have improved since our last technical report the numbers are still low to allow for adequate statistical power analysis. This has therefore delayed the start of testing efficacy of our select drugs that potentially target pathways linked to DEGs of our interest. We continue to collect gastric biopsy samples from stomach cancer patients, in the meantime we have evaluated expression of DEGs of our interest in a human gastric cancer cell line, MKN45. As shown in figure 3, these cells express our select DEGs of interest. These cells will be implanted into nude mice, subcutaneously or orthotopically and will be used to test efficacy of our drugs while we continue to collect more patient gastric biopsy samples.

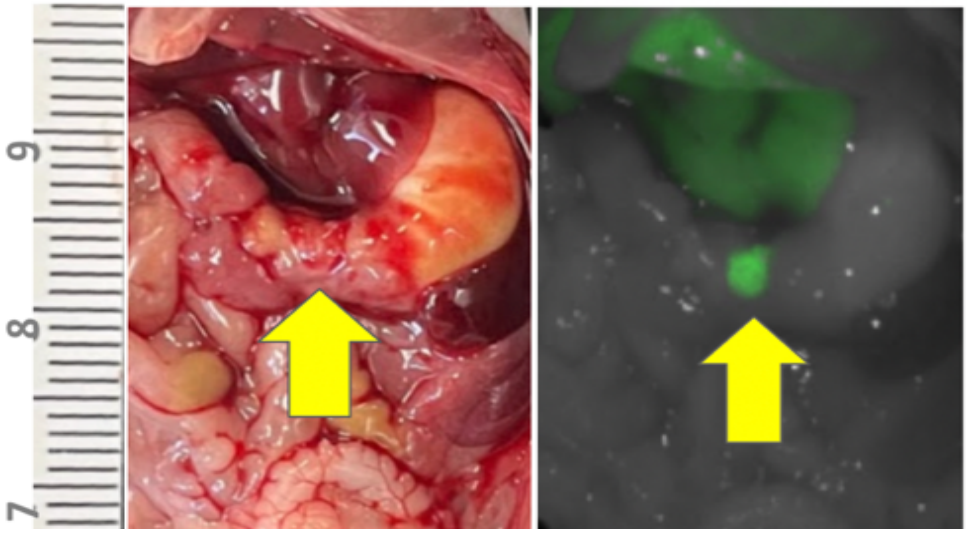

Fig. 2. Orthotopic model of patient gastric cancer. A nude mouse was orthotopically implanted with patient gastric biopsy tissue. Image on left is a bright light image of a mouse with an orthotopically implanted gastric tumor on the lesser curve of the stomach (indicated by the yellow arrow). The tumor is easier to appreciate in the image on the right with near infrared (NIR) imaging 96h after receiving TAG-72-IR800 dye. The tumor to background ratio (mean fluorescent intensity of the tumor/mean fluorescent intensity of surrounding normal tissue) is 2.22. The NIR imaging demonstrates distinct borders of the tumor. The model will be used for orthotopic implantation of fresh patient biopsy tissue.

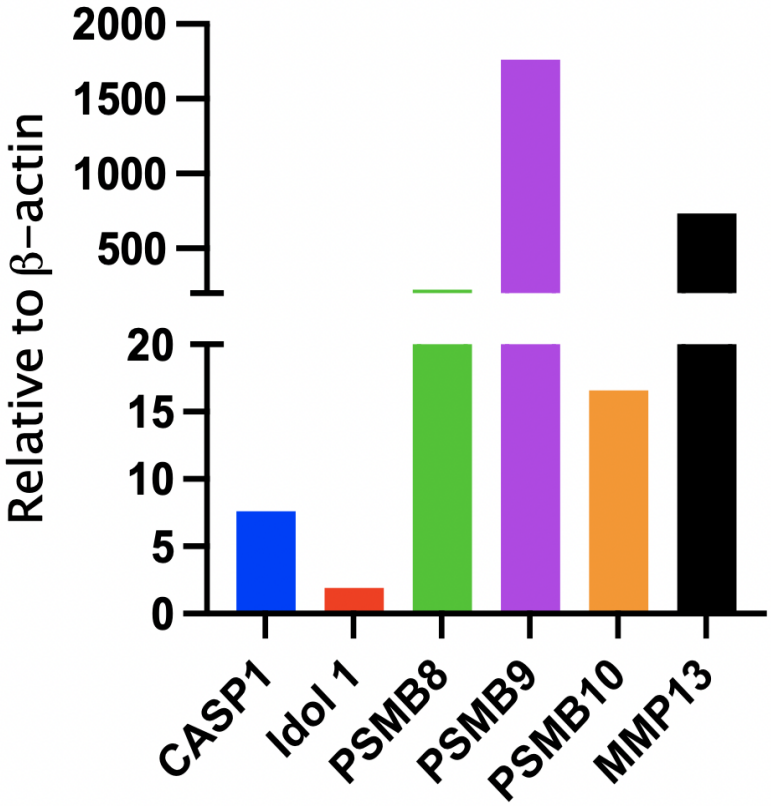

Fig. 3. Expression select DEGs in a human gastric cancer cell line, MKN45. Gene expression was quantified by qRT-PCR and expressed relative to GAPDH using comparative cycle threshold calculations (ΔC_T, Applied Biosystems).

What opportunities for training and professional development has the project provided?

Professional development involved presentation of the work at a conference, Digestive Disease Week, May 2022.

Hernandez, J, Turner, MA, Bali., P, Hosseini, M., Bouvet, M., Kelly, K., and **Obonyo, M.** Genomically silent refractory gastric cancer overexpress CXCL5.

How were the results disseminated to communities of interest?

Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?

With more patients coming in for gastric cancer surgeries, we plan to start drug treatments targeting select pathways of DEGs of interest. In the meantime, we will use a human gastric cancer cell line that will be implanted subcutaneously or orthotopically into nude mice for drug targeting studies. These experiments will also be used to optimize drug targeting conditions.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Our findings on a link between high expression levels of a chemokine, CXCL5 and the extent of malignancy, suggest that expression levels of CXCL5 could be used to determine patients more likely develop a fast progressing and aggressive disease. Pre-identifying patients at high risk of developing this disease phenotype will help with better stratification of patients that require quick intervention.

What was the impact on other disciplines?

Our results showing a strong association in expression levels of CXCL5 with an aggressive cancer involving *H. pylori* infection, which is inflammation driven maybe applicable to other inflammation-associated cancers.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

There are no changes in the approach and therefore, nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

Due to the COVID-19 pandemic we have not been able to harvest many gastric tumor biopsy samples as we had planned. This has affected drug targeting experiments that require many patient samples to achieve statistical power. However, due to availability of vaccines more patients have started scheduling gastric surgeries and therefore we anticipate we will collect more patient gastric cancer biopsy samples. In the meantime, we will use a human gastric cancer cell line, MKN45 for this drug targeting studies. These studies will also serve to optimize drug targeting conditions, which will therefore shorten experimental time when we embark on using patient gastric biopsy samples.

Changes that had a significant impact on expenditures

Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

Hernandez, J, Turner, MA, Bali., P, Hosseini, M., Bouvet, M., Kelly, K., and **Obonyo, M.** Genomically silent refractory gastric cancer in a young patient exhibits overexpression of CXCL5. Current Oncology. 2022;29:4725-4733.

- Yes, acknowledged federal support (Department of Defense award W81XWH-20-1-0675

Books or other non-periodical, one-time publications.

Nothing to Report.

Other publications, conference papers and presentations.

Presentation at a conference, Digestive Disease Week, 2022. Hernandez, J, Turner, MA, Bali., P, Hosseini, M., Bouvet, M., Kelly, K., and **Obonyo, M.** Genomically silent refractory gastric cancer overexpress CXCL5.*

- **Website(s) or other Internet site(s)**

Nothing to Report.

- **Technologies or techniques**

Nothing to Report.

- **Inventions, patent applications, and/or licenses**

Nothing to Report.

- **Other Products**

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS
What individuals have worked on the project?

Name:	Marygorret Obonyo
Project Role:	PI
Nearest person month worked:	3.6
Contribution to Project	Dr. Obonyo was involved in the design of experiments and overall supervision of the project.
Funding Support	
Name:	Michael Bouvet
Project Role:	Investigator
Nearest person month worked:	0.6
Contribution to Project	Dr. Bouvet alongside his lab staff assistant, Siamak Amirfakhri have generated the gastric cancer patient-derived orthotopic xenograft (PDOX) model.
Funding Support	
Name:	Kaitlyn Kelly
Project Role:	Investigator
Nearest person month worked:	0.6
Contribution to Project	Dr. Kelly has provided both involved and uninvolved patient gastric cancer specimens.
Funding Support	
Name:	Siamak Amirfakhri
Project Role:	Staff Research Assistant
Nearest person month worked:	2.4
Contribution to Project	Under supervision of Dr. Bouvet, Siamak Amirfakhri has generated the gastric cancer PDOX model.
Funding Support	
Name:	Michael Turner
Project Role:	MD Fellow
Nearest person month worked:	1.2
Contribution to Project	Dr. Turner has performed work related to the generation and maintenance of the gastric cancer PDOX model.
Funding Support	T32 NIH Training grant
Name:	Jonathan Hernandez
Project Role:	Staff Research Assistant
Nearest person month worked:	6
Contribution to Project	Under the supervision of Dr. Obonyo, Jonathan Hernandez has performed RNA extraction and RT-qPCR of patient gastric tissue fresh after surgery or stored at our biorepository.
Funding Support	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report.

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:

The following materials have been attached:

- An original copy of a journal article is attached.
- A presentation abstract for a conference.

References:

1. Banerjee A, Thamphiwatana S, Carmona EM, Rickman B, Doran KS, Obonyo M. 2014. Deficiency of the myeloid differentiation primary response molecule MyD88 leads to an early and rapid development of Helicobacter-induced gastric malignancy. Infect Immun 82:356-63.
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3. Bali P, Lozano-Pope I, Pachow C, Obonyo M. 2021. Early detection of tumor cells in bone marrow and peripheral blood in a fastprogressing gastric cancer model. Int J Oncol 58:388-396.
4. Mejias-Luque R, Lozano-Pope I, Wanisch A, Heikenwalder M, Gerhard M, Obonyo M. 2019. Increased LIGHT expression and activation of non-canonical NF-kappaB are observed in gastric lesions of MyD88-deficient mice upon Helicobacter felis infection. Sci Rep 9:7030.
5. Thamphiwatana S, Gao W, Obonyo M, Zhang L. 2014. In vivo treatment of Helicobacter pylori infection with liposomal linolenic acid reduces colonization and ameliorates inflammation. Proc Natl Acad Sci U S A 111:17600-5.

Current Oncology

Case Report

Genomically Silent Refractory Gastric Cancer in a Young Patient Exhibits Overexpression of CXCL5

Jonathan Hernandez [1], Michael A. Turner [2,3], Prerna Bali [1], Mojgan Hosseini [4], Michael Bouvet [2,3,5], Kaitlyn Kelly [2,3,5] and Marygorret Obonyo [1,5,*]

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Abstract: Gastric cancer is the third leading cause of cancer-related deaths, with more than one million new cases and approximately 841,000 deaths annually worldwide. We report a case of a young patient (25 years old) with an aggressive form of gastric cancer. The patient had previously been treated for *Helicobacter pylori* (*H. pylori*), which is a main risk factor for developing gastric cancer. Genetic testing showed an E-cadherin (*CDH1*) germline mutation of unknown significance. After eight cycles of chemotherapy, a positron emission tomography (PET) scan showed disease progression with an enlarging hypermetabolic right adnexal mass suspicious for metastatic disease. Tumor pathology demonstrated invasive and poorly differentiated gastric carcinoma. The analysis of the tumor biopsy indicated the very high expression of a chemokine, C-X-C motif chemokine 5 (CXCL5). The combination of *H. pylori* infection with an existence of a rare *CDH1* mutation could have contributed to this aggressive gastric cancer.

Keywords: young patient; advanced gastric cancer; *Helicobacter pylori*; CDH1; CXCL5

Citation: Hernandez, J.; Turner, M.A.; Bali, P.; Hosseini, M.; Bouvet, M.; Kelly, K.; Obonyo, M. Genomically Silent Refractory Gastric Cancer in a Young Patient Exhibits Overexpression of CXCL5. *Curr. Oncol.* **2022**, *29*, 4725–4733. https://doi.org/10.3390/curroncol29070375

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Accepted: 5 July 2022
Published: 6 July 2022

1. Introduction

Gastric cancer remains a significant global health burden as the third leading cause of cancer death and one of the most common, lethal [1], and recalcitrant malignancies [2,3]. *Helicobacter pylori* (*H. pylori)* infection is the main known risk factor for the development of gastric cancer. For most patients in the United States, gastric cancer is diagnosed in the locally advanced or late stages because screening is not performed, and the disease is only detected after the development of symptoms. Complete tumor resection, with or without adjuvant therapy, is the only curative treatment option, but only for eligible patients. As a result, most patients die within two years following operation. Most of these deaths are a consequence of gastric cancer recurrence and metastasis [3–6], with the peritoneum being the most common site of spread and treatment failure. The 5-year survival rate is less than 5% [7] after the cancer has metastasized, which has not changed significantly over the last 30 years. Despite multiple clinical trials of different treatment regimens [4,8], the prognosis remains poor for this disease. Although recent studies show that targeting the tumor microenvironment may help in developing new therapeutic treatments for gastric cancer, further studies need to be carried out to identify its complete potential [9]. In addition, even with recent advances in targeted treatments, which include trastuzumab, trastuzumab deruxtecan (T-DXd)-approved treatments for HER2-positive gastric cancer patients, and many other therapies under phase II and phase III trials, gastric cancer cure

rates remain low [10–13]. Recent data from a CYTO-CHIP (Cytoreductive surgery vs. Cytoreductive surgery and Hyperthermic Intraperitoneal Therapy) study provide some evidence of treatment efficacy for aggressive gastric cancer with peritoneal metastases [14]. Here, we report a case of an aggressive and lethal gastric cancer in a young patient.

2. Case Report

2.1. Clinical Course

A 25-year-old female presented to the emergency department with persistent abdominal pain after finishing a standard course of treatment for *H. pylori*. Her past medical history was notable for a 2-year history of intermittent abdominal pain with bloating and a 20 lb weight loss. She was discharged with pain medication after her emergency department work up showed mild hypokalemia and a 5 mm gallbladder polyp on a right upper quadrant ultrasound. A follow-up esophagogastroduodenoscopy (EGD) 5 months later revealed a gastric ulcer. Biopsies taken at the time of the EGD were positive for gastric adenocarcinoma. Her planned gastrectomy was aborted when, upon entering the abdomen, diffuse peritoneal disease was noted, consistent with stage IV disease. Germline genetic testing showed an E-cadherin (*CDH1*) mutation at 16q22.1 (FoundationOne CDx, Foundation Medicine, Inc. Cambrige, MA, USA). The mutation was considered a variant of unknown significance (VUS). The patient received systemic chemotherapy with epirubicin, oxaliplatin, and capecitabine. After eight cycles of chemotherapy, a positron emission tomography (PET) scan showed evidence of disease progression. The patient was started on a second-line chemotherapy regimen of leucovorin calcium and irinotecan hydrochloride (FOLFIRI). A repeat PET scan 3 months later showed overall stable disease, with persistent activity in the stomach as well as an enlarging hypermetabolic right adnexal mass (Figure 1). The patient was evaluated by the surgical oncology service and presented at the multidisciplinary tumor board. Because the patient had an overall stable disease on imaging and was doing well clinically, she was determined to be a candidate for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC). As part of her CRS/HIPEC procedure, the patient received a total gastrectomy with reconstruction and bilateral salpingo-oophorectomy as well as a distal pancreatectomy, splenectomy, and partial colectomy secondary to disease involvement. The peritoneal carcinomatosis index (PCI) was 11. The PCI is a quantitative measure of peritoneal disease burden that can range from 0 to 39, with lower numbers associated with improved survival [15].

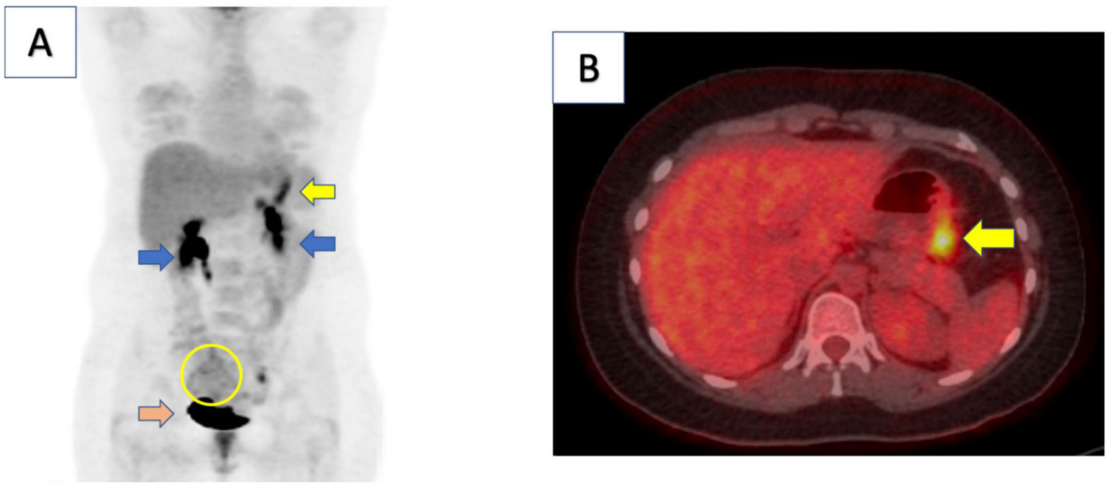

Figure 1. Computed tomography (CT)/positron emission tomography (PET) scan of patient demonstrated moderate focal uptake along gastric body consistent with known malignancy (yellow arrow in panel (**A**,**B**)). There was also a large, mildly hypermetabolic right adnexal area with heterogenous uptake concerning for metastatic involvement (yellow circle). Kidneys (blue arrows) and bladder (orange arrow) demonstrate physiologic uptake.

2.2. Pathology

Surgical pathology demonstrated invasive, poorly differentiated gastric carcinoma (Figure 2). The patient had an unremarkable recovery initially, but four months after surgery, she developed a left abdominal wall mass that was noted on interval imaging (Figure 3). During a brief hospitalization for partial small bowel obstruction, a biopsy of the mass confirmed disease recurrence. The patient received palliative radiation to her abdominal wall while hospitalized and was eventually discharged to home hospice. The patient passed away 8 months after surgery at 25 years of age.

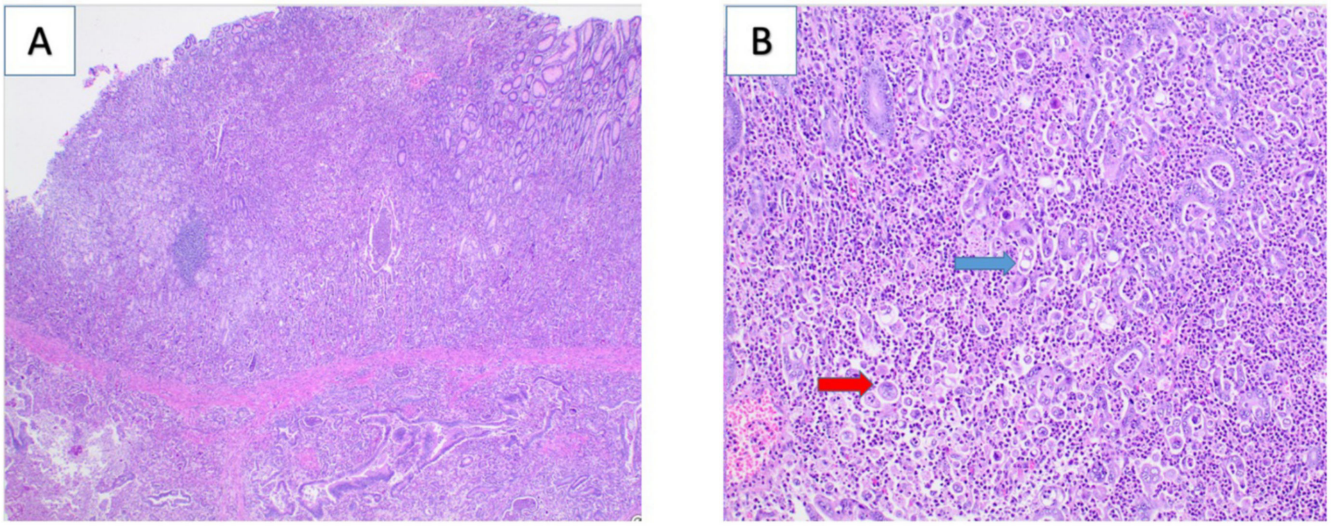

Figure 2. Hematoxylin and eosin staining revealed invasive, poorly differentiated gastric carcinoma invading into the muscularis propriawith minimal gland formation (panel (**A**),2× magnification). Panel (**B**) (20× magnification) demonstrates signet ring cell component (blue arrow) as well as pleomorphic neoplastic cells (red arrow).

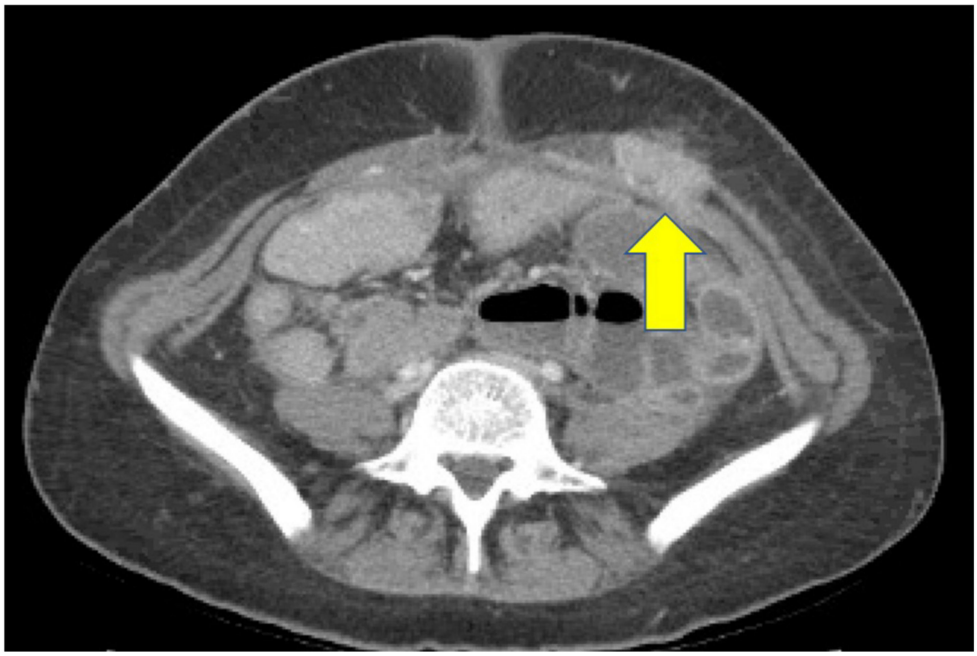

Figure 3. Axial CT image of case report patient demonstrated disease recurrence in left abdominal wall (yellow arrow).

The pathology of the patient tumor showed many neutrophils in the tissue surrounding tumor cells, which led us to examine the expression of C-X-C motif chemokine 5 (CXCL5). Several studies suggest that CXCL5 is a strong neutrophil chemoattractant [16–19]. In addition, the patient had been treated for *H. pylori* infection, which is associated with the increased production of CXC chemokines [20]. The goal was to further understand the status of the disease, either indicating the extent of disease severity/malignancy or host immunity to the tumor. Total RNA was isolated from the patient's gastric cancer tissue and processed for quantitative real-time polymerase chain reaction (qRT-PCR), as described in our previous studies [21–24], using the Direct-zol RNA mini kit (Zymo Research Corp) according to the manufacturer's instructions. RNA quality was determined by using a Nanodrop system (Thermo Fisher Scientific, Inc., Waltham, MA, USA) followed by reverse transcription into cDNA using the High Capacity cDNA Reverse Transcription kit (Thermo Fisher Scientific, Inc.). The specific primer pairs used in the study for CXCL5 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were as follows: forward 5′-TGGACGGTGGAAACAAGG-3′; reverse, 5′-CTTCCCTGGGTTCAGAGAC-3′ [25] and forward, 5′-CCTGGTCACCAGGGCTGC-3′; reverse, 5′-CCGTTCTCAGCCTTGACGG-3′ (Integrated DNA Technologies, Inc., Clareville, IA, USA), respectively. The expression of CXCL5 for each sample was expressed relative to its GAPDH using comparative cycle threshold calculations (ΔC_T, Applied Biosystems, Waltham, MA, USA) and plotted using GraphPad Prism software. Including this case, we examined the expression of CXCL5 in a series of 13 other gastric tissue samples obtained from the UCSD Cancer Center Biorepository and new presenting patients at our center for comparison. All patients provided written informed consent and were followed up. The additional gastric tissue samples for comparison included 13 gastric cancer tumor tissues (T). A summary of all patients and their gastric tumor characteristics, including the case patient (2T), are provided in Table 1. There was very high expression of CXCL5 in the tumor of the case patient (Figure 4). Among the gastric tissue samples we analyzed, only one other sample from an older patient (10T) had significant CXCL5 levels (over 2-fold relative to GAPDH). However, the levels were much lower than the levels observed in the patient described in this case report.

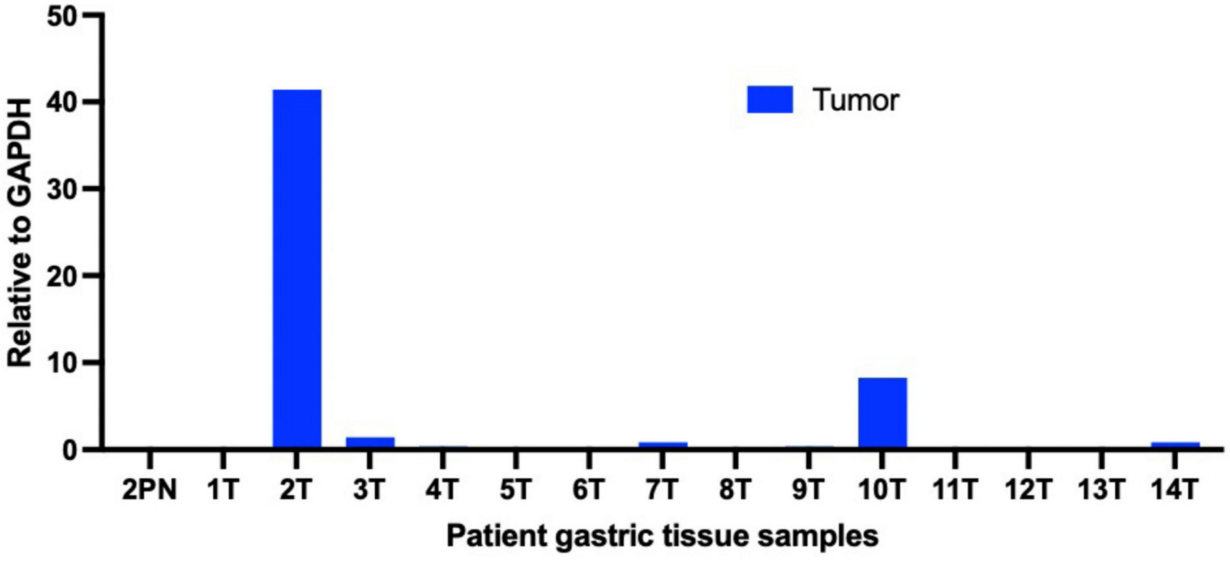

Figure 4. CXCL5 was overexpressed in the gastric biopsy of the case patient. CXCL5 expression in 13 other gastric biopsies is shown for comparison. CXCL5 expression was quantified via qRT-PCR and expressed relative to GAPDH using comparative cycle threshold calculations (ΔC_T, Applied Biosystems). 2PN, paired normal control of case patient (2T); T, tumor gastric cancer tissue.

Table 1. Characteristics of gastric cancer patients.

Patient ID	Patient Sex	Patient Age	Patient Race/ Ethnicity	Primary	Grade	Metastatic	Stage	Chemotherapy
2PN	F	25	Hispanic	Adenocarcinoma, diffuse type	G3: poorly diff	Yes	IV (ypT4bypN3bypM1)	EOX/FOLFIRI
1T	F	53	Asian	Adenocarcinoma, signet ring-cell	G3: poorly diff	No	IIA (ypT3ypN0)	EOX
2T	F	25	Hispanic	Adenocarcinoma, diffuse type	G3: poorly diff	Yes	IV (ypT4bypN3bypM1)	EOX/FOLFIRI
3T	M	66	Asian	Adenocarcinoma, residual	G3: poorly diff	No	IIA (ypT3N0)	EOX and chemorads with capecitabine
4T	M	51	White	Adenocarcinoma	G3: poorly diff	No	IIB (ypT4aN0)	Yes (unspecified in notes)
5T	M	78	White	Invasive adenocarcinoma	G3: poorly diff	Yes	IIIC (pT4aN3a)	No
6T	F	49	White	Invasive adenocarcinoma, signet ring	G3: poorly diff	Yes	IIB (pT4aN0)	No
7T	M	69	Hispanic	Adenocarcinoma	G3: poorly diff	Yes	IV (ypT4bN3bM1)	FOLFOX
8T	F	48	Asian	Adenocarcinoma, diffuse type. Signet-ring	G3: poorly diff	No	IIIC (pT4aN3a)	No
9T	F	81	Vietnamese	Gastric adenocarcinoma, intestinal type	Moderate to poorly differentiated	Invades serosa	pT4aN0	No
10T	M	81	Asian	Gastric adenocarcinoma	G3: poorly differentiated	Yes	ypT3N3a	FOLFOX
11T	F	83	Hispanic	Gastric adenocarcinoma	G3: poorly differentiated	No	mpT2N3a	No
12T	M	73	White	Gastric adenocarcinoma	G3: poorly differentiated, undifferentiated	No	ypT3N1	FLOT/FOLFOX (neoadjuv)
13T	F	66	Asian	Gastric adenocarcinoma, diffuse type with signet ring	G3: poorly differentiated, undifferentiated	No	ypT4aN0	FLOT
14T	F	66	White	Gastric adenocarcinoma with signet ring cell	G3: poorly differentiated	Yes	pT4aN3b	No

2PN = paired normal control of case patient (2T), T = tumor gastric cancer tissue, EOX = epirubicin, oxaliplatin, capecitabine, FOLFIRI = folinic acid, fluorouracil, and irinotecan, FOLFOX = folinic acid, fluorouracil, and irinotecan, FLOT = fluorouracil, leucovorin, oxaliplatin, and docetaxel.

3. Discussion

This is a very rare case of early-onset, aggressive, poorly differentiated gastric carcinoma without a well-characterized pathogenic germline alteration. Gastric cancer is a disease that primarily affects older adults with a median age of 68 years at diagnosis in the United States [26,27]. The diagnosis of gastric cancer is often delayed as patients present with non-specific abdominal complaints. Upper GI endoscopy is the preferred method for the evaluation of a suspicious gastric lesion as it allows for tissue diagnosis [28]. Endoscopic ultrasound (EUS) was thought to be more sensitive for staging gastric cancer in the T and N stage; however, with advances in computed tomography (CT) imaging techniques, CT imaging is just as accurate [29–32]. As such, CT imaging is now the most common imaging technique for the staging of gastric cancer as it can assess tumor invasion, lymph node involvement, and the presence of distant metastasis [28]. PET/CT is also useful for assessing metastatic disease or recurrence [28]. However, a high number of patients are still found to have metastatic disease upon staging laparoscopy, which was unappreciated in cross sectional imaging [33]. One series from Memorial Sloan Kettering found that as many as 37% of patients thought to have localized gastric cancer with CT or endoscopic ultrasound, had metastatic disease discovered with a staging laparoscopy [34].

There are two classification systems for the histology of gastric cancer: Lauren's criteria and the World Health Organization (WHO) system. Lauren's criteria divides gastric cancer into two types: intestinal and diffuse type [35]. The intestinal type is more often associated with environmental risk factors and more often affects older males [35]. The diffuse type is more often associated with genetic risk factors and more often affects younger patients and females [35]. Of the two, the diffuse type has a worse prognosis. The WHO classification system identifies four major types of gastric cancer histology: tubular, papillary, mucinous, and poorly cohesive, with tubular pathology being the most common [35]. The WHO classification also recognizes several less common histological types: adenosquamous carcinoma, squamous carcinoma, hepatoid adenocarcinoma, carcinoma with lymphoid stroma, choriocarcinoma, parietal cell carcinoma, malignant rhabdoid tumor, mucoepidermoid carcinoma, Paneth cell carcinoma, undifferentiated carcinoma, mixed adeno-neuroendocrine carcinoma, endodermal sinus tumor, embryonal carcinoma, pure gastric yolk sac tumor, and oncocytic adenocarcinoma [35]. The case patient's histologic type was described as a poorly differentiated/diffuse carcinoma.

We showed the overexpression of CXCL5 in the gastric tumor of the case patient. There is some recent evidence from clinical studies indicating that chemokines may play an important role in the development and progression of gastric cancer [36,37]. Certain chemokines, therefore, may potentially function as future biomarkers to stratify treatment for patients. The expression of CXCL5 has been implicated in the pathogenesis and progression of several solid tumors, including colorectal cancer [38,39], breast cancer [40], hepatocellular carcinoma [19], bladder cancer [41], pancreatic cancer [42], lung cancer [43], prostate cancer [44], and gastric cancer [18,45–48]; however, these were in older patients. Among the 14 gastric tumor tissue samples we analyzed, the expression of CXCL5 was greatest in the gastric tissue biopsy from the case patient. To our knowledge, this is the first report of high CXCL5 expression in a young gastric cancer patient. Given that this was a young patient with a histologically diffuse tumor type, the implication is likely that this could be related to genetic predisposition. It is possible that the current *CDH1* VUS could turn out to be of particular importance in aggressive gastric cancer. The accumulation of similar cases in the future will allow for further analysis of this observation. In addition, given that the patient had been treated for *H. pylori*, it is possible that the combination of *H. pylori* infection and the presence of this yet unproven, but possibly putative pathogenic *CDH1* germline alteration contributed to the fast and aggressive form of gastric cancer in this patient.

In conclusion, this was a rare case of a young patient with a germline *CDH1* VUS with advanced gastric cancer that proved to be refractory to existing therapies, including systemic and intraperitoneal chemotherapy and complete cytoreduction. The tumor ex-

hibited the very high expression of CXCL5. This is a hypothesis-generating association, and further investigations to determine if there is a link between CDH1 alterations and CXCL5 overexpression are warranted. Such an association may provide further insight into genomically silent, treatment refractory, and poorly differentiated gastric cancer.

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Genomically Silent Refractory Gastric Cancer Overexpress CXCL5

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Gastric cancer is a common and lethal cancer, with approximately a million new diagnosed cases and 841,000 deaths annually worldwide. The majority of human stomach tumors are associated with chronic infection with the bacterial pathogen *Helicobacter pylori* (*H. pylori*). For most patients in the United States, gastric cancer is diagnosed in the locally-advanced or late stages because screening is not performed and disease is detected only after the development of symptoms. Despite multiple trials of different treatment regimens, prognosis remains poor. In addition, there is currently no way to predict which patients will or will not have a response to chemotherapeutic agents. We previously identified differentially expressed genes (DEGs) associated with rapid and accelerated *Helicobacter*-induced gastric cancer progression using our unexpected model of gastric cancer we termed fast "progressors". This model, which involves infection of mice deficient in myeloid differentiation primary response gene 88 (*Myd88*$^{-/-}$) with *H. felis* (a close relative of the human gastric pathogen *H. pylori*) progressed expeditiously to gastric cancer in situ compared to the standard gastric cancer model (*H. felis*-infected C57BL/6 wild type mice). One of the DEGs that was highly expressed in our fast "progressor" model was the (C-X-C motif) ligand 5 (CXCL5). This chemokine has been shown to be involved in tumor growth, metastasis, and angiogenesis. Here we report that high expression of CXCL5 is associated with fast progressing and aggressive gastric cancers in human subjects. We analyzed stomach samples from gastric cancer patients and healthy subjects by quantitative real-time polymerase chain reaction (qRT-PCR). We found that the expression level of CXCL5 was linked to the extent of malignancy. In particular, overexpression of CXCL5 was associated with genomically silent and refractory gastric tumors. Tumors from these patients were poorly differentiated and patients had a significantly lower survival rate compared to patients with tumors that had low CXCL5 expression levels. Our data suggest that expression levels of CXCL5 could be used to determine patients more likely develop a fast progressing and aggressive disease. Pre-identifying patients at high risk of developing this disease phenotype will help with better stratification of patients that require quick intervention.