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# Paraneoplastic Leukemoid Reaction in Gastroesophageal Junction Adenocarcinoma: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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**Conflict of interest:** None declared

**Patient:** Female, 72-year-old
**Final Diagnosis:** Paraneoplastic leukemoid reaction
**Symptoms:** Anemia
**Medication:** —
**Clinical Procedure:** —
**Specialty:** Oncology

**Objective:** Rare disease

**Background:** The presence of leukocytosis associated with non-hematological malignancy after ruling out other causes is defined as paraneoplastic leukemoid reaction (PLR). PLR is a rare manifestation of various solid tumors. It is associated with poor prognosis unless receiving effective antineoplastic treatments.

**Case Report:** A 72-year-old female was referred to a hematologist/oncologist for the evaluation of leukocytosis with neutrophilia. Initial workup was unremarkable; however, she had progressively worsening leukocytosis with neutrophilia, associated with severe anemia and dysphagia. Computed tomography (CT) scan revealed wall thickening at the gastroesophageal junction (GEJ) and multiple hypodensities of the liver. Esophagogastroduodenoscopy (EGD) confirmed the diagnosis of GEJ tumor and biopsy returned as adenocarcinoma with human epidermal growth factor receptor 2 (HER2) overexpression. Leukocytosis resolved after the first round of chemotherapy and the patient remains progression-free with the addition of trastuzumab to her chemotherapy regimen.

**Conclusions:** We report a rare case of PLR caused by GEJ adenocarcinoma. This is the first case of PLR in a patient with metastatic GEJ adenocarcinoma with HER2 overexpression in the Caucasian population. It is important to workup leukocytosis promptly, to keep malignancy in the differential diagnosis and to seek early hematology/oncology consultation.

**MeSH Keywords:** Esophagogastric Junction • Genes, erbB-2 • Leukemoid Reaction • Neoplasms • Paraneoplastic Syndromes

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## Background

Paraneoplastic leukemoid reaction (PLR) is a rare manifestation of nearly all non-hematological malignancies and has been reported in case reports and case series. The condition is associated with poor prognosis unless receiving effective antineoplastic treatments [1,2]. PLR remains a diagnosis of exclusion after ruling out other causes, such as infection, hematological malignancy, and medications (e.g., glucocorticoids and exogenous growth factors).

The incidence of PLR is reported as 1% to 4% [1] with a poorly understood pathophysiology. Proposed mechanisms include paracrine secretion of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) by tumors to stimulate their own growth and pro-inflammatory cytokines (interlukin-6, interleukin-1α) in response to tumor progression or necrosis [1,3–6].

G-CSF producing primary or metastatic upper gastrointestinal cancers (esophageal, gastric, and gastroesophageal junction [GEJ]) are extremely rare but have been reported in a few cases in Japan, which could be one of the potential causes for PLR [6]. In this study, we report a rare presentation of a patient with progressive leukocytosis with neutrophilia as well as severe anemia secondary to PLR.

## Case Report

A 72-year-old Caucasian female with a past medical history of chronic kidney disease, gastroesophageal reflex disease, remote history of peptic ulcer disease, and 60+ pack-year smoking history was referred to a hematologist/oncologist by her primary care physician in May 2018 for the evaluation of leukocytosis with neutrophilia.

The patient complained about mild and intermittent discomfort in the left upper quadrant. She reported the discomfort was similar to her duodenal ulcers in the past, which she attributed to "stress" and was well controlled with omeprazole daily. She denied any melena, hematochezia, or changes in bowel habits. There were no signs of infection or recent illness. The complete blood count at her initial encounter revealed a total leukocyte count of 25 600/uL with absolute neutrophil of 21 000/uL and monocyte of 1500/uL, hemoglobin of 11.8 g/dL, and platelets of 282 000/uL. Other pertinent laboratory results were blood urea nitrogen of 34 mg/dL, baseline creatinine level 1.8 to 2.0 mg/dL, elevation of alkaline phosphatase of 324 U/L, normal total bilirubin, lactic dehydrogenase of 228 U/L, and uric acid of 10.3 mg/dL.

Initial hematological workup, including peripheral smear, JAK2 V617F mutation, and BCR/ABL, revealed no evidence of leukemia or other myeloproliferative neoplasms. In late July 2018, subsequent bone marrow biopsy and aspiration were performed secondary to worsening leukocytosis. Left-shifted maturation was seen, and differential count was as follows: segmented neutrophils 18%, band neutrophils 30%, metamyelocytes 18%, myelocytes 11%, eosinophilic cells 2%, monocytic cells 3%, and lymphocytes 6%. For the next few months, the patient had worsening leukocytosis 48 200/uL with neutrophilia (42 400/uL) associated with severe anemia (6.6 g/dL). She also complained of progressively worsening dysphagia to solid foods, unintentional weight loss of 20 pounds, and fatigue. CT chest/abdomen/pelvis ordered by her hematologist/oncologist days prior to admission, showed significant wall thickening at GEJ with nodular abnormality projecting into the proximal stomach and multiple hypodensities of the liver (Figure 1A).

The patient was admitted to our hospital in early September 2018 for workup of symptomatic anemia. At the time of admission, she complained about chronic dry cough and shortness of breath upon exertion. She denied any melena, hematochezia, hematuria, nose bleeding, abdominal pain, fever, chills, or wounds. She never had esophagogastroduodenoscopy (EGD) done for her peptic ulcer disease. Family history was significant, a daughter with rectal cancer at the age of 48 years old. She was afebrile with a blood pressure of 105/49 mmHg, regular heart rate, normal respiratory rate, and normal oxygen saturation on room air. Physical examinations revealed a thin and chronically ill-appearing female with diminished breath sounds throughout. The rest of the physical examination was unremarkable. Laboratory results were pertinent for leukocytosis (50 500/uL) with neutrophilia (48 200/uL) and immature myelocytes (500 u/L each for bands, metamyelocytes, and myelocytes), creatinine 2.2 mg/dL (baseline 1.8–2.0), hyponatremia at 131 mmol/L, hypochloremia at 90 mmol/L, normal CO2, albumin 3.3 g/dL, alkaline phosphatase 320, total bilirubin at 1.8 mg/dL, and normal lactate.

Sepsis workup, including a urinalysis, respiratory panel, and blood cultures, was negative for any infectious etiology. Chest x-ray showed mild nodular opacities in the mid and lower lung, and right base. Procalcitonin was elevated at 2.95 ng/mL (normal <0.09 ng/mL). Repeat peripheral smear revealed marked absolute neutrophilia and macrocytic anemia without blasts, basophilia, significant left shift, or dysplastic features. Two units of packed red blood cells were transfused along with intravenous (IV) fluid.

EGD revealed a fungating mass at the GEJ without active bleeding (Figure 1B). Histopathology revealed an adenocarcinoma with HER2 overexpression (immuohistochemical score 3+). Port was placed prior to discharge. During her hospital





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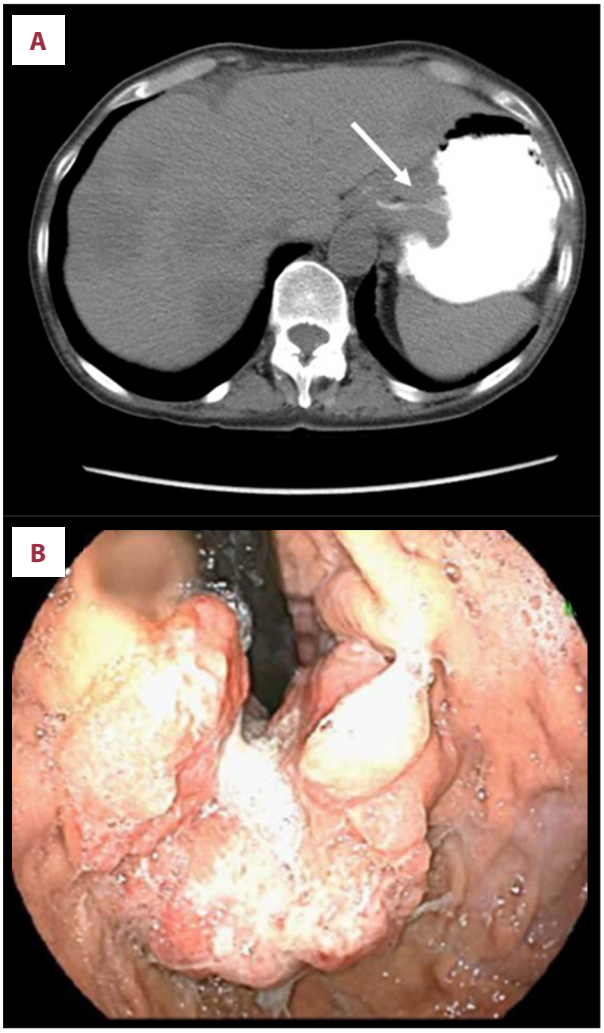


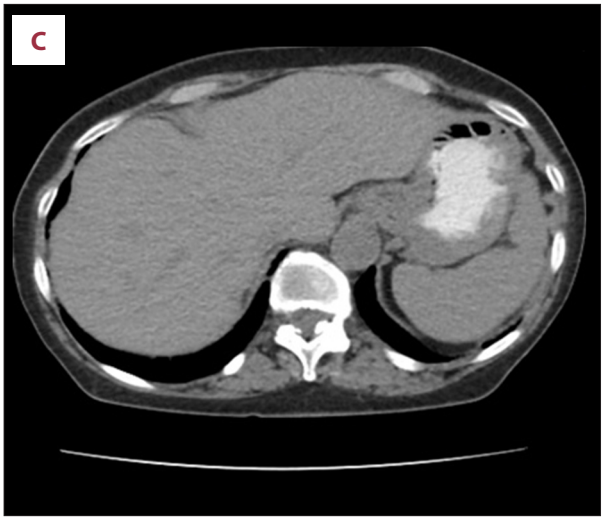


**Figure 1.** Axial computed tomography (CT) images and esophagogastroduodenoscopy (EGD) in a 72-year-old female. (**A**) Initial CT showed significant wall thickening at gastroesophageal junction (GEJ) with nodular abnormality projecting into the proximal stomach (white arrow) and multiple hypodensities of the liver. (**B**) EGD showed fungating mass at GEJ. (**C**) CT showed improving gastric cardia mucosal thickening and decrease in hepatic metastasis 6 months after initiation of chemotherapy.

stay, the patient was started on IV piperacillin/tazobactam for presumed pneumonia with temperature up to 39.4°C the day after admission. She was discharged home with amoxicillin/clavulanate to complete the course of treatment. Her leukocytosis and neutrophilia improved to 30 100/uL and 25 900/uL on the day of discharge, respectively. Systemic therapy was recommended for advanced GEJ adenocarcinoma based on the National Comprehensive Cancer Network (NCCN) guidelines. FOLFOX (folinic acid/fluorouracil/oxaliplatin) was initiated a week and half after being discharged from the hospital. Leukocytosis completely resolved after 1 round of FOLFOX. Trastuzumab was later added to her chemotherapy after a normal echocardiogram. Patient remained progression-free. Repeat CT scan 6 months after initiation of therapy, showing improving gastric cardia mucosal thickening and decrease in hepatic metastasis (Figure 1C). Her G-CSF level was not obtained as it was not available in our institution. Trends of her white blood cells (WBCs) with neutrophils corresponding to the major events can be seen in Figure 2A. Of note, WBCs were plotted after the effect of exogenous growth factors dissipated.

## Discussion

PLR is a rare manifestation of various non-hematological tumors and has rarely been described in the gastrointestinal system. This is the first case of PLR in a patient with metastatic GEJ adenocarcinoma with HER2 overexpression in the Western literature. No precise value of leukocytosis is utilized to clearly define PLR; however, WBC count >20 000 to 50 000/uL has been described in the literature as leukocytosis [4]. Neutrophils are generally the predominant types in PLR as seen in this case (Figure 2A); however, eosinophils have been reported in pancreatic adenocarcinoma and thyroid cancer [4]. Interestingly, monocytosis is also observed in our case (Figure 2B). A previous study examining leukocytosis and neutrophilia for locally advanced esophageal cancer demonstrates that monocytosis promotes tumor cells to spread in the circulation under inflammatory conditions [2]. In our patient gradual increase in monocytes (within in 4 months) might be one of the contributing factors for the rapid progression of the disease.

Large-scale studies are very few in the literature due to the rarity of PLR. Granger et al. conducted a retrospective single-center study (N=3770) to investigate the incidence of PLR by examining the patients with WBC counts >40 000/uL from 2005 to 2008. They found the incidence of PLR to be 10% (N=77) in 758 patients with solid tumors, which was more prevalent than the previously reported 1 to 4% [1]. Among those 758 patients





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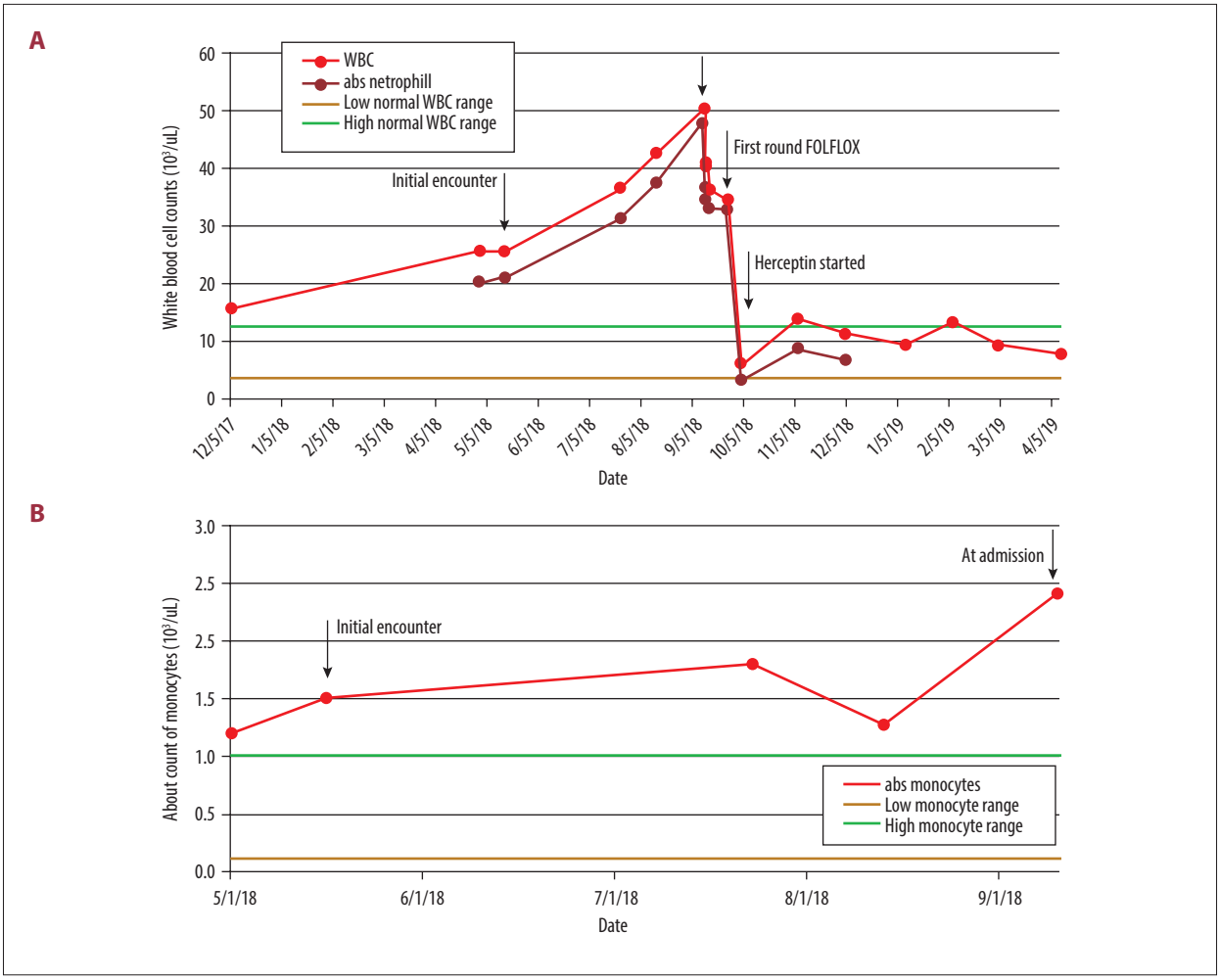


**Figure 2.** Blood count trend in a 72-year-old female. (**A**) Absolute counts of neutrophils. (**B**) Absolute counts of monocytes from initial encounter to the admission.

with solid tumors, infection was documented in 15% (n=112) with nearly half of them diagnosed with pneumonia and 25% of them with multiple sources of infection. The study concluded that infection was an uncommon cause of extreme leukocytosis for patients with solid tumors. They reasoned that PLR is probably underreported because their inclusion criteria did not accommodate for the possibility of multiple etiologies [1]. As a result, it is essential to keep non-hematological malignancy as a differential diagnosis until ruling out other causes.

Fever is the most common symptom for paraneoplastic syndromes [7]. Hoshimoto et al. compiled 21 cases of G-CSF producing upper gastrointestinal cancers and pyrexia was observed in 7 of these 21 cases [6]. In contrast, 99% of patients were afebrile despite extreme leukocytosis and tumor burden per Granger et al. [1]. Our patient had 1 episode of fever up to 39.4°C in addition to elevated procalcitonin and bilateral infiltrates seen on CT scan. A course of antibiotics was given for presumed bacterial pneumonia, making her leukocytosis improve from 50 500/uL to 36 500/uL which was her new baseline leukocytosis prior to the chemotherapy. Procalcitonin has been a valuable assay to identify bacterial infection and guide antibiotic therapy. It is unclear the utility of procalcitonin in cancer patients with or without PLR, especially for our patient with significant renal impairment. Panel et al. found no difference in serum C-reactive protein and procalcitonin levels between the infection and paraneoplastic fever [8]. In contrast, procalcitonin may be valuable to distinguish bacterial infection for patients with advanced urological cancer [9]. More research is required to examine the effectiveness of procalcitonin in cancer patients who present with fever.

G-CSF producing upper gastrointestinal cancers are extremely rare and clinical characteristics of this entity remains unclear [6]. Hoshimoto and colleagues reported a 72-year-old Japanese female with GEJ adenocarcinoma, pT3N1M0 (stage II B), with HER2+who underwent gastrectomy followed by adjuvant S-1 (oral fluoropyridine). Normal serum G-CSF and



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leucocytes were observed at the time of gastrectomy. During her follow-up post-operatively, patient was found to have progressive leukocytosis (peaked at 47 680/uL) with neutrophilia along with significant elevation of G-CSF level (779 pg/mL; normal, <39 pg/mL), which were attributed to new metastatic liver and pulmonary lesions Interestingly, the elevation completely normalized within a week post-hemihepatectomy, though immunohistochemical staining by using anti-G-CSF antibody was negative on the metastatic liver lesion. They explained that a more aggressive course can be seen at the metastatic site than the primary lesion, in which a subset of cancer cells acquire the ability to produce G-CSF, making it a possible explanation for rapid growth of metastatic liver lesions as seen in their case [6]. On the contrary, our patient shares similar histopathology but with more extensive disease process at the time of diagnosis, making her a non-surgical candidate. To our knowledge, measurement of serum G-CSF is not commonly obtained nor available in our institution; however, it may be useful for prognostic purposes and monitoring disease for the patients with PLR. The possibility of expression of G-CSF and its functional receptors have been confirmed in bladder cancer cells [10].

Several case reports found that short-term and long-term prognosis for the patients with PLR were poor. About 76% of patients died within 3 months of presentation and only 10% who received therapies were alive at 1 year [1]. Yu et al. reported that a patient with PLR attributed to esophageal adenocarcinoma. Leukocytosis resolved within a week after esophagectomy and remained free of progression for 6 months [11]. In a retrospective study, Schernberg et al. found that leukocytosis and neutrophilia were independent prognostic factors of poor overall survival, progression free survival, and locoregional control for patients with advanced esophageal squamous cell carcinoma [2]. In our case, the patient's leukocytosis with neutrophilia completely resolved after the first round of chemotherapy and remained stable with the addition of trastuzumab. The frequency of HER2 overexpression in gastric or GE cancer ranges from 4.4% to 53.4% with a mean of 17.9% [12]. The prognosis of gastric and GEJ cancer with HER2 positive is mixed; however, a phase 3, ToGA (trastuzumab for gastric cancer), demonstrated the superiority of trastuzumab in combination with chemotherapy compared with chemotherapy alone in terms of overall survival for 13.8 months and 11.1 months, respectively [13]. It may be interesting to have more studies to demonstrate the relationship between PLR and HER2.

## Conclusions

PLR is a rare manifestation of non-hematological malignancy, associated with very poor prognosis. It is important to work-up leukocytosis promptly to keep malignancy in the differential diagnosis as well as seeking early hematology/oncology consultation.

### Acknowledgement

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### Conflicts of interest

None.

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