Leukocytosis Associated with Esophageal Squamous Cell Carcinoma as a Predictor of Poor Prognosis - A Case Report and Review of Literature

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Abstract Leukocytosis, specifically granulocytosis in malignancy is a common finding with various etiologies. Granulocytosis associated with esophageal cancer has not commonly been reported in case reports in the United States. Furthermore, granulocyte colony stimulating factor (G-CSF) producing tumors have been associated with a variety of cancers. However, G-CSF producing esophageal tumors are rare. The diagnosis is established through serum G-CSF levels and immunohistochemistry staining of tumor cells. Here, we report a case of a 72-year-old woman with persistent granulocytosis leading to the diagnosis of esophageal squamous cell carcinoma (ESCC). Although, our case did not report serum G-CSF levels, we strongly suspect it to be the underlying etiology in our case. Additionally, through our missed opportunity, we hope to emphasize and increase awareness of G-CSF producing ESCC.

Keywords: esophageal squamous cell carcinoma, leukocytosis, granulocyte colony stimulating factor (G-CSF)


1. Case Presentation

A 72-year-old Caucasian female with history of left breast cancer status post mastectomy in 2003, hypertension, hyperlipidemia, osteopenia and chronic kidney disease was referred to the hematologist in September 2017 for evaluation of leukocytosis. The patient’s white blood cell count (WBC) was first noted to be elevated on routine blood work in March 2017 at a value of 15.9 x 10³/µL. Differentials were as follows; absolute neutrophil count 11.5 x 10³/µL, absolute immature granulocytes 0.2 x 10³/µL, elevated monocytes at 1.2 x 10³/µL and absolute lymphocyte count 2.8 x 10³/µL. Hemoglobin and platelet count were at 13.5 g/dL and 529 x 10³/µL respectively. Complete blood count was repeated in April 2017, WBC had decreased to 12.0 x 10³/µL with a similar differential profile. The patient did not report any symptoms of an infection. A thorough workup including imaging studies did not reveal an infectious etiology.

CBC was repeated in 4 months with WBC notable for 18.4 x 10³/µL with ANC of 13.5 x 10³/µL. On evaluation by a hematologist in September, the patient reported intentional weight loss of 12 pounds and fatigue for the last 6 months. She denied any pain, recent fevers or infections. Physical exam did not reveal lymphadenopathy or hepatosplenomegaly. Peripheral smear revealed neutrophilia with no immature cells. BCR-ABL and JAK-2 mutation were checked and both resulted negative. A bone marrow biopsy was performed, the results of which showed normocellular marrow (30%) with myeloid hyperplasia and no dysplasia or increase in blasts. Due to persistent elevation of WBC count [Figure 1], an ultrasound of the abdomen was done to rule out splenomegaly with the intention to obtain CSF3R to rule out chronic neutrophilic leukemia. Abdominal ultrasound was notable for adenopathy immediately posterior to the left hepatic lobe, superior to the celiac artery. Computed tomography (CT) of the abdomen and pelvis further confirmed adenopathy. PET/CT showed a long segment esophageal mass extending from the level of the carina down to the gastroesophageal junction, concerning for esophageal malignancy with hypermetabolic adenopathy in the retro-crus region and abdomen. The patient underwent an esophagogastroduodenoscopy (EGD) which revealed a fungating mass 25-30 cm. Biopsy revealed invasive moderately to occasional poorly differentiated squamous cell carcinoma. Therapy was not initiated due to poor performance status. Several weeks following her diagnosis, the patient had recurrent admissions for hypercalcemia. Her hospitalization course was complicated by persistent encephalopathy with subsequent death 2 months following diagnosis.
Figure 1. Illustrating the presence of leukocytosis with neutrophilia 6 months preceding the diagnosis of esophageal cancer and increasing white blood cell counts with progression of cancer.

2. Discussion

Granulocytosis in malignancy is a well described paraneoplastic phenomenon seen in up to 30% of patients with solid tumors. It occurs more frequently in lung and gastrointestinal tumors but has also been seen with breast cancer, brain tumors, genitourinary carcinomas [1].

Leukocytosis associated with malignancy is attributed to many causes; infiltration of the bone marrow by tumor cells, a concomitant inflammatory process such as necrosis of the tumor mass and or infection and finally production of granulopoietic factors by neoplastic cells [1,2]. Our review focuses on the latter etiology of leukocytosis in esophageal squamous cell carcinoma (ESCC) as we suspect that our patient’s elevated white blood cell count is likely related to secretion of granulopoietic factors by tumor cells, based on elimination of other etiologies.

Granulocyte colony-stimulating factor is a hematopoietic growth factor that regulates the production of granulocytes [2]. These cytokines are produced by macrophages, endothelial cells and fibroblasts in direct response to toll-like receptors signaling, and in response to cytokines such as TNF. They signal through JAK/STAT-coupled receptors.

Early studies by Robinson et al, through a series of experiments demonstrated a directly proportional relationship between elevated serum and urine CSF levels and white blood cell counts in patients with various neoplasms [2]. However, at that point, it was unclear whether G-CSF production was mediated by the host body’s response to a growing neoplasm versus secretion by the malignant cells. [2] Hocking et al further validated the production of G-CSF by the human neoplastic cells through cell lines derived from patients with leukocytosis. [1] Furthermore, the degree of granulocytosis tends to correlate to tumor burden.

The diagnostic criteria for G-CSF-producing tumors has been defined as (1) a marked increase in the leukocyte counts, (2) elevated G-CSF activity, (3) a decrease in leukocyte counts following tumor resection, and (4) the verification of G-CSF production in the tumor.

A review of the medical literature in English revealed 19 case reports associated with esophageal squamous cell carcinoma [Table 1] [3-19]. All the cases have occurred in Japan. We report a case of esophageal squamous cell carcinoma where persistent leukocytosis preceded the diagnosis of cancer by up to 6 months. Analysis of previously reported cases show that most of the cases were predominantly older male patients. The degree of leukocytosis at the time of diagnosis was typically above $15,000 \times 10^3/\muL$. G-CSF levels were elevated in all the cases. G-CSF level was not obtained in our patient however we presume it was likely elevated in the setting of persistent granulocytosis and absence of an infection.

Several cases also demonstrated elevated C-reactive protein and interleukin-6 levels. Four of the cases including our case had hypercalcemia without bone metastases in addition to leukocytosis. All the cases, excluding our case, as it was not tested, had accompanying elevated parathyroid hormone related peptide (PTHrp) levels.
Table 1.

<table>
<thead>
<tr>
<th>Case</th>
<th>Author</th>
<th>Age in years</th>
<th>Gender (M/F)</th>
<th>Leukocytosis $\mu$L</th>
<th>G-CSF pg/mL</th>
<th>G-CSF IHC</th>
<th>Site of distant metastases</th>
<th>Therapy</th>
<th>Calcium mg/dl</th>
<th>PTHrP pm</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fukuda</td>
<td>50</td>
<td>M</td>
<td>27,100</td>
<td>60.2</td>
<td>Positive</td>
<td>Choroidal</td>
<td>CRT</td>
<td>-</td>
<td>-</td>
<td>3 months-dead</td>
</tr>
<tr>
<td>2</td>
<td>Kitani</td>
<td>92</td>
<td>F</td>
<td>23,500</td>
<td>131</td>
<td>Positive</td>
<td>None</td>
<td>Radical esophagectomy</td>
<td>-</td>
<td>-</td>
<td>Alive at 18 months</td>
</tr>
<tr>
<td>3</td>
<td>Mayanagi</td>
<td>30</td>
<td>M</td>
<td>19,020</td>
<td>53.7</td>
<td>Positive</td>
<td>Aorta, LN</td>
<td>CRT, esophagectomy</td>
<td>-</td>
<td>-</td>
<td>3 months-recurrence</td>
</tr>
<tr>
<td>4</td>
<td>Watanabe</td>
<td>81</td>
<td>F</td>
<td>22000</td>
<td>1175</td>
<td>NM</td>
<td>Liver</td>
<td>Resection, CRT</td>
<td>7.7</td>
<td>94.5**</td>
<td>0.5 months-died</td>
</tr>
<tr>
<td>5</td>
<td>Ota</td>
<td>63</td>
<td>M</td>
<td>124,000</td>
<td>286</td>
<td>Positive</td>
<td>None</td>
<td>Esophagectomy</td>
<td>-</td>
<td>-</td>
<td>NM</td>
</tr>
<tr>
<td>6</td>
<td>Yamaguchi</td>
<td>60</td>
<td>M</td>
<td>25,100</td>
<td>292</td>
<td>Positive</td>
<td>None</td>
<td>Palliative stent placement</td>
<td>-</td>
<td>-</td>
<td>3 months-died</td>
</tr>
<tr>
<td>7</td>
<td>Nakata</td>
<td>56</td>
<td>M</td>
<td>24,300</td>
<td>78</td>
<td>Positive</td>
<td>Liver</td>
<td>Radical resection, CRT</td>
<td>15.3</td>
<td>6.5**</td>
<td>19 months-Alive</td>
</tr>
<tr>
<td>8</td>
<td>Ichiishi</td>
<td>66</td>
<td>M</td>
<td>33,900</td>
<td>180</td>
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<td>None</td>
<td>Supportive care</td>
<td>-</td>
<td>-</td>
<td>2 months-died</td>
</tr>
<tr>
<td>9</td>
<td>Matsamoto</td>
<td>66</td>
<td>M</td>
<td>41,500</td>
<td>154</td>
<td>Positive</td>
<td>Lang</td>
<td>Resection, CRT</td>
<td>-</td>
<td>-</td>
<td>16 months</td>
</tr>
<tr>
<td>10</td>
<td>Kato</td>
<td>54</td>
<td>M</td>
<td>16,900</td>
<td>150</td>
<td>Positive</td>
<td>Liver</td>
<td>Chemotherapy Upper limit of normal</td>
<td>High**</td>
<td>-</td>
<td>3 months-died</td>
</tr>
<tr>
<td>11</td>
<td>Komatsu</td>
<td>73</td>
<td>M</td>
<td>45,710</td>
<td>231</td>
<td>Positive</td>
<td>None</td>
<td>Radical resection</td>
<td>-</td>
<td>-</td>
<td>19 months-Alive</td>
</tr>
<tr>
<td>12</td>
<td>Mimatsu</td>
<td>69</td>
<td>M</td>
<td>19,600</td>
<td>113</td>
<td>Positive</td>
<td>Lung, Liver</td>
<td>Radiation therapy</td>
<td>-</td>
<td>-</td>
<td>7 months-dead</td>
</tr>
<tr>
<td>13</td>
<td>Tanabe</td>
<td>76</td>
<td>M</td>
<td>24,260</td>
<td>134</td>
<td>Positive</td>
<td>None</td>
<td>Radical esophagectomy, CRT</td>
<td>-</td>
<td>-</td>
<td>10 months-dead</td>
</tr>
<tr>
<td>14</td>
<td>Shimakawa</td>
<td>70</td>
<td>M</td>
<td>16,700</td>
<td>254</td>
<td>Positive</td>
<td>None</td>
<td>Neoadjuvant chemotherapy Radical Esophagectomy, Chemotherapy</td>
<td>-</td>
<td>-</td>
<td>12 months-dead</td>
</tr>
<tr>
<td>15</td>
<td>Oshikiri</td>
<td>65</td>
<td>M</td>
<td>15,900</td>
<td>140</td>
<td>Positive</td>
<td>None</td>
<td>Radical Esophagectomy</td>
<td>-</td>
<td>-</td>
<td>3 months-alive</td>
</tr>
<tr>
<td>16</td>
<td>Eto</td>
<td>59</td>
<td>M</td>
<td>38,780</td>
<td>241</td>
<td>NM</td>
<td>None</td>
<td>Esophagectomy</td>
<td>-</td>
<td>-</td>
<td>13 months-alive</td>
</tr>
<tr>
<td>17</td>
<td>Eto</td>
<td>58</td>
<td>M</td>
<td>52,000</td>
<td>197</td>
<td>NM</td>
<td>Cardiac LN</td>
<td>Neoadjuvant chemotherapy, Esophagectomy</td>
<td>-</td>
<td>-</td>
<td>17 months-alive</td>
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<tr>
<td>18</td>
<td>Eto</td>
<td>75</td>
<td>M</td>
<td>26,200</td>
<td>239</td>
<td>NM</td>
<td>Present (Not specified)</td>
<td>Chemotherapy</td>
<td>-</td>
<td>-</td>
<td>3 months-alive</td>
</tr>
</tbody>
</table>

**tumor cells stain positive for anti-PTHrP

CRT: Chemoradiotherapy

NM: not mentioned

A profound finding, which is consistent is the poor prognosis associated with leukocytosis. Typically, esophageal SCC is associated with a median progression free survival of 9.7 months [20]. The average survival time appears to be shorter for patients with G-CSF production and leukocytosis; approximately 3 months in several of the cases reported. It is established that the neutrophil-lymphocyte ratio is associated with poorer survival rates [21]. There are several mechanisms through which granulocytosis has been hypothesized to lead to worse outcomes. Broadly, chronic inflammation through generation of inflammatory cytokines (IL-1 and IL-6) suppresses anti-tumor immunity [22]. Furthermore, this may play a role in cancer related cachexia leading to debilitation and poorer outcomes. Interestingly, some tumor cells also express G-CSF receptors leading to increased tumor growth via an autocrine effect [23]. G-CSF is known to stimulate angiogenesis via JAK2/STAT3 pathway thereby promoting aggressive and chemo-resistant tumors [23]. There are also ongoing studies on the role of neutrophil extracellular traps (NETs) in the role of metastases [24].

In the cases where surgical resection of localized esophageal cancer was possible, a subsequent decline or normalization of WBC count was seen following resection. However, high rates of recurrence were seen and an incremental response in WBC count was associated with the recurrence of cancer. Further studies are needed to clarify an appropriate treatment strategy for G-CSF producing ESCC.

This report highlights an important association between leukocytosis and ESCC secondary to G-CSF production. Although, G-CSF levels were not obtained in our case, we strongly suspect the diagnosis of GSCF producing ESCC. All the cases reported in Japan reported G-CSF levels, therefore this concept should be familiarized in the United States and serum G-CSF and immunohistochemistry staining should be routinely employed in patients with granulocytosis in the setting of malignancy.
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References


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