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Paraneoplastic Leukemoid Reaction as a Marker of Tumor Progression in Non-Small Cell Lung Cancer

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Key Terms

paraneoplastic leukemoid reaction; G-CSF; lung cancer; tumorigenesis; RAS/RAF/MEK

INTRODUCTION

The presence of leukocytosis associated with solid tumors has been documented for many decades.¹ The first demonstration that it was the tumor itself producing a colony-stimulating agent came in 1977 when Asano et al. demonstrated that serial transplantation of human lung cancer tissue from a patient with neutrophilia into mice caused neutrophilia in recipient mice as well.² The formal definition of a leukemoid reaction is a white blood cell (WBC) count $>50,000/\text{mm}^3$ with a predominance of neutrophil precursors. When this elevation in the WBC count is associated with malignancy it is termed a paraneoplastic leukemoid reaction (PLR).³ The differential diagnosis of leukemoid reaction includes infection, hematologic malignancy, iatrogenic origin (e.g. steroids, growth factors), solid tumor spread to bone and PLR. Two different case series have reviewed the frequency of PLR. Granger et al. evaluated 3770 consecutive solid tumor patients and found that, of the 758 patients with extreme leukocytosis, 77 (10%) of these patients had PLR. Interestingly, only 13 of the 77 patients (17%) had non-small cell lung cancer (NSCLC), but 41 (53%) patients overall had

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tumors involving the lungs.⁴ Kasuga et al. evaluated a series of 227 patients with lung carcinoma and identified 33 (14.5%) patients with PLR. They also found that 16 patients showed elevated serum granulocyte colony-stimulating factor (G-CSF) levels with 12 tumors staining positive for G-CSF by immunohistochemistry (IHC).⁵ Another notable finding of the elevated WBC count in these case series and other case reports is that leukemoid reactions are predictive of a poor prognosis. In a study by Granger et al., 76% of patients diagnosed with PLR died within 12 weeks. Other series and case reports have noted similar prognostic information.^{5,3}

Here we report the first description, to our knowledge, of non-small cell adenocarcinoma of the lung that evolved during treatment to have a PLR that was responsive to both systemic treatment and radiation therapy.

CASE HISTORY

A 51-year-old man initially presented with a protracted period of cough, night sweats, recurrent fevers and weight loss. He was a lifelong never-smoker and had no significant past medical history and no family history of malignancy.

After several recurrences of pneumonia, imaging studies ultimately thoracic lymphadenopathy, a mass right hilar mass, and a superior segment mass. He underwent a diagnostic CT guided biopsy and a staging PET/CT scan and was diagnosed with T4N2M0 (stage IIIb) adenocarcinoma of the lung. At the time of presentation, his WBC count was 12,000/mm³.

He started treatment with weekly carboplatin and paclitaxel for five weeks with concurrent intensity modulated radiotherapy (IMRT) to 50.4Gy. During this treatment, his WBC count was 4,300–10,700/mm³. A PET/CT scan 2 months after initiation of treatment demonstrated osseous progression. He then began treatment with cisplatin and pemetrexed. He tolerated this therapy well and had a normal WBC count (Figure 1, days 0–200). He subsequently started on pemetrexed maintenance therapy for 2 cycles. After cycle 2, he began noting right neck/ supraclavicular swelling. A PET/CT scan demonstrated worsening of hypermetabolic soft tissue tumor burden, and elevated bone marrow fluorodeoxyglucose-avidity (FDG). Increased bone marrow FDG avidity can be seen in reactive marrow responding to chemotherapy, growth factor, or tumor infiltration along with other less likely processes. Additionally, his WBC count began rising (Figure 1, days 200–240). The leukocytosis primarily consisted of neutrophils, although there was a left-shift with some band neutrophils, metamyelocytes, myelocytes and promyelocytes present. He was initiated on a clinical trial of gemcitabine in combination with MLN8237, a second-generation Aurora A kinase inhibitor that is thought to act by inhibiting mitosis by acting on the mitotic spindle and is predicted to cause cytopenias. Patients on this trial were not given growth factor support or glucocorticoid treatment. During this treatment, the WBC count, which had been rising, normalized after each cycle but again increased prior to the next cycle. WBC values during this period are shown in Figure 1 (days 240–300) and included: Pre-Cycle 1 WBC 35,300/mm³ (91.4% PMN/bands); Cycle 1 Day 12 WBC 9,300/mm³ (90.6% PMN/bands); Pre-Cycle 2 WBC 55,500/mm³ (85% PMN/bands); and Cycle 2 Day 18 WBC 10,400/mm³

(93.3% PMN/bands). Imaging after cycle 2 demonstrated interval disease progression in bones and soft tissue. For example, the right neck lesion noted above increased from $2.8 \times 3\text{cm}$ to $5.3 \times 4.7\text{cm}$. He stopped the clinical trial due to disease progression. He then received palliative radiation to his neck lesion (30Gy over 10 fractions), for tumor related pain. This temporarily improved his symptoms, however, with the next imaging study done 21 days after radiation the lesion had increased to $5.5 \times 6.3\text{cm}$. There was a marked decrease in his WBC count from $94,300/\text{mm}^3$ (96% PMN/bands with left shift) to $31,100/\text{mm}^3$ (96.1% PMN/bands with left shift) (Figure 1, days 300–330) during radiation treatment. After radiation, his WBC count again began to increase (Figure 1, days 331–340). Following radiation therapy for local palliation, he enrolled in a clinical trial of the anti-PD-L1 antibody to address worsening systemic disease burden, and his WBC count again dropped during therapy (Figure 1, days 340–360). CT scan of the chest after his second infusion showed tumor progression in his thoracic lymph nodes. With all three treatments, which act through different mechanisms, the patient experienced reduction in WBC counts after treatment; however, the pace of tumor cell growth ultimately outpaced any therapeutic benefit. Due to his progressive and symptomatic disease he elected to pursue hospice treatment and expired shortly thereafter.

To determine the etiology of the leukocytosis, he was first evaluated for an infectious process. The work-up, including bacterial, fungal, and viral cultures, was negative. In regards to iatrogenic causes, he was not receiving glucocorticoids or growth factor support. We also evaluated his peripheral smear and performed a bone marrow biopsy for evidence of marrow invasion by adenocarcinoma or evidence of a primary hematologic malignancy (chronic myelogenous leukemia or another myeloproliferative neoplasm), and we did not find evidence of either process. His peripheral smear on day 305, when his WBC count was $94,300/\text{mm}^3$ (96.1% PMN/bands), demonstrated a myeloid cell left shift with mostly mature cells and no blasts. His red blood cells were normochromic and normocytic. There were dacrocytes, rare schistocytes and reticulocytopenia. He had thrombocytosis with some large forms. His bone marrow was hypercellular with trilineage hematopoiesis. Flow cytometry demonstrated a predominance of T-cells within the lymphoid gate. There was no increase in blasts, aberrant marker expression, or evidence of a primary hematologic neoplasm. Molecular PCR evaluation for the JAK2 V617 mutation and BCR-ABL transcripts were both negative.

Finally, after ruling out a primary bone marrow process and marrow infiltration by NSCLC, we tested the patient's serum for endogenous levels of granulocyte-monocyte colony-stimulating factor (GM-CSF), G-CSF, interleukin-1 alpha (IL-1 α) and interleukin-6 (IL-6). His serum GM-CSF and IL-1 α levels were normal, his serum IL-6 level was mildly elevated at 10pg/ml (0–5pg/ml) and his serum G-CSF was significantly elevated at 507pg/ml (0–39.1pg/ml). These results corresponded to a WBC count of $48,700/\text{mm}^3$ (Day 318). G-CSF is produced by endothelium, macrophages and other immune cells. Given that the WBC decreased in response to tumor directed treatments, it is most likely that the bulk of the identified G-CSF originated from tumor cells.

Finally, endobronchial tumor tissue (Figure 2a) was assayed by immunohistochemistry (IHC) for G-CSF expression (anti-G-CSF antibody, clone 3D1, catalog number sc-53292,

Santa Cruz Biotechnology, Inc., Dallas, TX). Infiltrating tumor cells diffusely stained positive for G-CSF, while surrounding normal tissue and controls were negative for G-CSF staining (Figure 2b). Given these results he was diagnosed with a PLR caused by tumor production of G-CSF.

DISCUSSION

Prior studies have identified a causative relationship between elevated WBC count and cytokines produced by the tumor cells. Studies in cell lines, mouse models and human tumor tissues have demonstrated that one possible mechanism of G-CSF upregulation is through RAS/RAF/MEK pathway activation. Currently, MEK inhibitors are an active area of clinical development for use as cancer therapeutics.⁶ G-CSF has been demonstrated to be important for granulocyte mobilization, possibly through expansion and mobilization of CD11b+Gr1+ myeloid cells that produce tumorigenic factors such as Bv8, matrix metalloproteinases, and TGF-beta. Increases in this CD11b+Gr1+ myeloid cell population may facilitate tumor cell invasion at sites of metastasis.^{6,7} This has primarily been demonstrated in mice with breast cancer lung metastases; however, elevated levels of G-CSF-regulated myeloid cells and Bv8 expression in infiltrating neutrophils have been identified in human lung adenocarcinoma, indicating that this may be a more generalizable mechanism of metastasis.^{8,9}

Although much of this work has yet to be translated to lung cancer, the case presented here and the increased frequency of PLR in NSCLC compared with other cancers provide a compelling justification for investigation of this pathway in lung cancer.⁴ Additionally, given the molecular pathways underlying PLR and the possible implications for progression of disease, it may be reasonable to move beyond using the WBC count (when not impacted by myelosuppressive or supportive treatments) as a prognostic marker and investigate it and G-CSF as surrogate markers for tumor cell death. This may allow treatment monitoring at a molecular level, which current imaging modalities are not able to provide.

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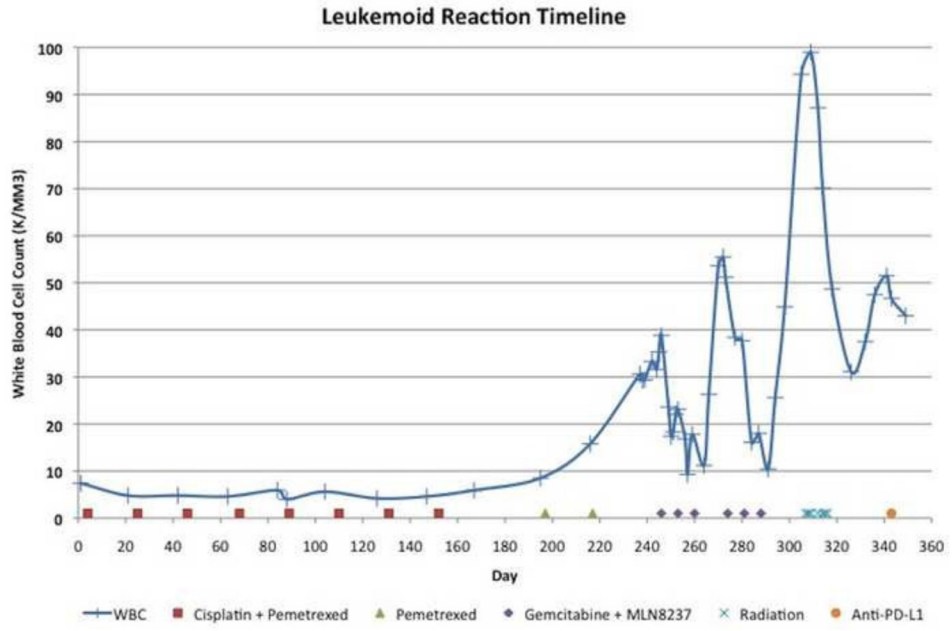


Figure 1. Correlation of WBC with anti-neoplastic therapy. WBC is expressed as $10^3/\text{mm}^3$. Anti-neoplastic treatments are also shown. Day number is from the time of diagnosis.

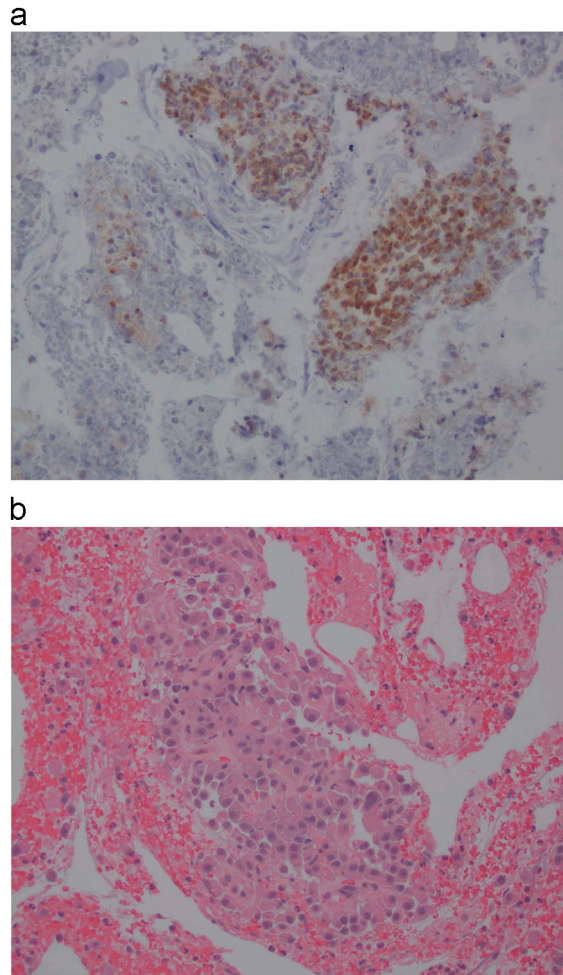


Figure 2. Endobronchial biopsy of patient's right lung mass demonstrating involvement by NSCLC cells expressing G-CSF. Representative images (20× magnification) of hematoxylin and eosin staining (a) and immunohistochemical staining with anti-G-CSF antibody (b) are shown. Images are from the same area of the biopsy. Note brown staining indicating G-CSF expression in tumor cells, while normal lung tissue without tumor involvement does not stain positive for G-CSF expression (b).