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Hyperleukocytosis in Metastatic Solid Tumors, A Benign Paraneoplastic Syndrome of Poor Prognosis: Short Review of Literature

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Abstract

Leukemoid reaction describes an important leukocytosis (more than 50,000 white blood cells/mm³) with increased early neutrophil precursors. It is secondary to a physiologic stimulation of the bone marrow in most of the cases. It is called paraneoplastic when it is the consequence of cytokine storm induced by malignant processes. Many solid tumors have been associated with paraneoplastic leukocytosis in the literature. The elevated white blood cells (WBC) count is a benign process by itself, but it is associated with bad prognosis and dramatic evolution of the underlying neoplasms. After reviewing the literature concerning the Paraneoplastic Leukemoid Reaction (PLR), case reports and small case series, I am writing a small review in order to increase the clinicians' awareness about this rare but serious condition. It is considered an indirect marker of poor outcome.

Keywords: Paraneoplastic; Leukemoid reaction; Metastatic Solid tumors

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Introduction

Paraneoplastic syndromes are symptoms seen in certain malignancies and are not related to the direct invasion of the cancer. They occur through secretion of humoral factors (cytokines or hormones) or via inducing immune responses against the tumor[1]. Leukemoid reaction is defined as a leukocytosis caused by a physiologic stimulation of the bone marrow secondary to stress (severe hemorrhage), infection, certain drugs (mainly Dapsone, Sulfa drugs, growth factors, corticosteroids) or malignancy[2]. The leukocytosis usually exceeds 50,000 WBC/mm³, with predominance of early non clonal neutrophil precursors (myelocytes and metamyelocytes), along with band forms[2,3]. Thus, in the paraneoplastic leukemoid reaction (PLR), the tumor cells will release cytokines, stimulating the bone marrow and leading to hyperleukocytosis.

PLR is characterized by the proliferation of all the normal myeloid elements in the bone marrow in contrast to acute leukemia where the most immature elements (promyelocytes and myeloblasts) predominate. Bone marrow examination is of little help in evaluating the patient with neutrophilia, except in certain conditions of leukemoid reactions associated with leukoerythroblastosis or the presence of immature cells (blasts and other cells more immature than the metamyelocytes) on the peripheral blood smear. In case of PLR, the bone marrow will be hypercellular, but otherwise unremarkable.

Solid tumors are associated with cytokine storm: a secretion of inflammatory factors, chemokines and other molecules or hormones that will act in a generalized way. Different systems will be affected: endocrine, neurological, muco-cutaneous and hematological systems. Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), Granulocyte Colony Stimulating Factor (G-CSF), interleukin (IL)-1, IL-6 and Tumor Necrosis Factor (TNF)-α have been implicated in PLR. Among these, G-CSF is the most potent cytokine inducing hyperleukocytosis[4-7].

PLR has been associated with many non-hematologic malignancies with a prevalence varying between 15 and 30% of tumors[8]. Almost all histologic subtypes of malignancies of malignancies were reported in the literature as being associated with this syndrome, including carcinoma of the lung, colon, rec-

tum, stomach, brain, liver, pancreas, breast, ovary, kidney and melanoma[3,8,9]. The most common reported solid tumors were non-small cell lung cancer (35%)[8], specially squamous cell subtype[9], skin cancers, metastatic pancreatic adenocarcinoma and sarcomas.[3]. Patients developing lung and liver metastases were seen to have an associated leukemoid reaction, with a hypothesis that extensive epithelial lining of the lungs and liver makes tumor involvement at these levels more likely to produce G-CSF[10].

Paraneoplastic leukocytosis is usually associated with an inflammatory anemia and paraneoplastic hypercalcemia, but even without these findings, it's correlated with a poor patient outcome. A possible hypothesis is that the circulating neutrophils might be an important source of Vascular Endothelial Growth Factor (VEGF), which expression has been linked with tumor invasiveness, increased recurrence and progression rates, particularly in urothelial carcinomas[11,12]. Furthermore, over stimulated WBC by cytokines and G-CSF have a potent reciprocal proliferative effect on the tumor cells. Granulocyte mobilization is possibly through expansion and mobilization of CD11b+Gr1+ myeloid cells. These latter produce tumorigenic factors such as Bv8, matrix metalloproteinases, and transforming growth factor (TGF)-beta, which facilitate tumor cell invasion at the sites of metastases[13,14].

Resolution of the hyperleukocytosis may occur after adequate anti-neoplastic agents, as well as the response to treatment may be assessed by following the WBC count.

Large population studies concerning PLR are few in the literature. Granger and colleagues underwent one of the largest scale studies: a retrospective review identifying 758 patients with solid tumors from 2005 - 2008 in a single institution center of 3770 patients. The incidence of PLR defined as a WBC count of more than 40000/mm³ was 10 %. The majority of the patients (68%) had a bulky, generalized metastatic disease upon radiologic evaluation. However, infectious etiologies were rare. Remarkably, most of the patients were hemodynamically stable at their initial presentation, but their short-term and long-term prognoses were poor with 78% of the patients either dead or discharged to hospice within 12 weeks of their initial extreme leukocyte count. Only 10 % of the patients were alive at 1 year interval, knowing that they have received adequate cytotoxic treatment[15]. Moreover, Chakraborty reported a case of poorly differentiated metastatic carcinoma associated with PLR. In his discussion and review of literature, he described PLR as a "paracrine mechanism" used by tumor cells to stimulate their own growth, highlighting its correlation with poor outcome and tumor relapse, sometimes preceding the radiological objective recurrence[16,17].

Conclusion

In conclusion, PLR can explain the important leukocytosis seen in cancerous patients. Extremely elevated WBC count in non-hematologic malignancies remains a diagnosis of exclusion. Although it has been infrequently due to infectious etiologies, infections among other causes of physiologic and malignant bone marrow stimulation should be ruled out. As a single process, the hyperleukocytosis has no lethal effect, but it is associated with high tumor burden and disease activity, thus poor prognosis and clinical outcomes.

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