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INVITED COMMENTARY

Cancer inflammation and inflammatory biomarkers: can neutrophil, lymphocyte, and platelet counts represent the complexity of the immune system?

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Despite the fact that the link between cancer and inflammation was first suggested by Virchow in the 19th century, it has only been in the last 15 years that our understanding of this link has reached the point where therapeutic interventions are possible [1–3]. Inflammation is known to be both a cause and a consequence of cancer. For example, chronic inflammation due to infectious diseases is believed to be responsible for more than 15% of known cancers to date [4], while inflammatory mediators are known to directly promote malignant transformation in experimental models [5]. On the other hand, once cancer progresses, it leads to a chronic inflammatory-like state which, through altered aminoacid metabolism among other mechanisms [6] causes cachexia, the main cause of death in patients with cancer.

Given that multiple immune and inflammatory markers are part of routine laboratory testing their use as prognostic and predictive biomarkers has been extensively examined. For example a low absolute lymphocyte count (ALC), generally <1.5 or 1.2×10^9/l, is prognostic of poor survival in the setting of multiple cancers such as non-Hodgkin's lymphoma, chronic lymphocytic leukemia, acute leukemia, head and neck cancer, cancers of the ovary, breast, colon, pancreas, lung, as well as sarcomas [7–12]. Moreover, low ALC is predictive of poor response to chemotherapy in colorectal, lung, and breast cancer [10]. In addition to single markers, such as ALC, prognostic scores based on combining various inflammatory markers have been developed. Examples include the modified Glasgow prognostic score (C-reactive protein and albumin) [13], the prognostic index (C-reactive protein and white cell count) [14], the neutrophil to lymphocyte ratio (NLR), and the platelet to lymphocyte ratio (PLR). Out of these biomarkers the NLR, which has been examined in over 60 studies, has been shown to be prognostic of outcomes in multiple cancers [15]. For example, a recent meta-analysis in patients with colorectal cancer, which included 16 studies, showed that an increased NLR is indeed associated with poor survival [16].

Efforts in developing such inflammatory biomarkers have also been made in hepatocellular carcinoma (HCC) following resection, trans-arterial chemoembolization, or liver transplantation. Halazun *et al.* [17] showed that among 150 patients undergoing liver transplantation for

HCC those with an NLR above five had a significantly lower overall survival (5-year survival, 28% vs. 64%, $P = 0.001$) and NLR was the only significant factor in predicting disease-free survival in multivariate analysis. Six additional studies (four of them very recent) have now supported the role of the increased NLR as a powerful prognostic marker of HCC recurrence following liver transplantation, although they used different cutoffs ranging from ≥3 to ≥5 [18–23].

In the study by Lai *et al.* [24] in this issue of Transplant International, NLR, as well as PLR, was examined as a prognostic biomarker in 181 patients undergoing liver transplantation for HCC. Indeed, an increased NLR (≥5.4), in agreement with older and current literature, was again prognostic of poor survival in these patients (5-year survival rate of 48.2% vs. 64.5%). The novelty of the current study resides in the use of the NLR as a predictor of dropout from the waiting list. The last NLR measurement, performed just before transplantation or dropout, but not the initial value at the time of listing, nor the slope, was the best predictor of dropout of all parameters examined (43% for NLR ≥5.4 vs. 21% for NLR <5.4). While this study introduces an inflammatory biomarker, such as the NLR, as a possible predictor of dropout, its clinical utility at the current time is limited by the fact that the information, if validated, is available to the clinician too late. Clearly however, examination of NLR as a predictor of dropout should be examined in prospective studies in which regular measurements during the waiting list period are taken because there is a real need for the identification of such biomarkers.

A limitation in the use of peripheral blood inflammatory markers for the prognostication of HCC patients undergoing transplantation is the fact that inflammation due to hepatitis infection, hepatic cirrhosis, or the use of immunosuppressive drugs post-transplantation will inadvertently have an impact on these markers irrespective of tumor biology. As a result, the composition of the inflammatory milieu at the site of the tumor microenvironment, while not easily accessible, may be more informative of tumor biology than peripheral blood markers. The prognostic ability of the intratumoral immune infiltrate has now been shown in all major cancers and is probably best exemplified in colorectal cancer where the immune infiltrate at the primary tumor site of more than 400 patients was prognostically superior to clinical parameters including the TNM stage [25]. This means that information from the immune infiltrate can provide prognostic information superior to the size of the cancer (T) or the lymph nodes metastasis status (N) [26]. In the liver transplantation field, Unitt *et al.* [27] showed that reduced lymphocytic infiltration in HCC tumors and a high intratumoral CD4 to CD8 ratio were independent prognostic factors of poor outcome, consistent with the hypothesis that a reduced number of cytotoxic CD8+ effector T lymphocytes at the tumor site is a sign of poor immunological reactivity to the malignant cells.

Furthermore, it is now clear that the inflammatory reaction associated with cancer is a largely ineffective antitumor response and that the local tumor environment is often infiltrated by immunosuppressive as well as tumor growth-promoting cells [28,29]. Antitumor effector immune-type cells include cytotoxic CD8+ T cells, NK cells, NKT cells, Th1 helper cells, and M1 macrophages, which secrete and are supported by cytokines such as IL-2, TNF-α, and IFN-γ. Among immunosuppressive and tumor supporting cells, which are recruited into tumors, are the T regulatory cells, myeloid-derived suppressor cells, Th2 helper cells, and tumor-associated macrophages. These immunosuppressive cells secrete and are supported by cytokines such as IL-10, TGF-β and VEGF, and their presence in tumor tissues of HCC patients is well documented [30–33]. Interestingly, although they can exert both tumor-promoting and tumor-killing functions, intratumoral neutrophils are a poor prognostic factor in HCC [34]. A further complicating issue is the expression by both immune cells and cancer cells of immune inhibitory ligands and other immunosuppressive molecules such as PD-L1, B7-H3, B7-H4, Gal-9, indoleamine 2, 3-dioxygenase (IDO), all of which inhibit antitumor immune responses and are currently the target of new cancer drugs [35].

Clearly routine laboratory tests, such as ALC, C-reactive protein, and composites such as the NLR or other inflammatory indices, cannot capture the complexity of cancer inflammation and cancer immune responses or accurately represent tumor biology. In addition, knowledge of the immune interactions at the tumor microenvironment can provide clinicians with targets for treatment in an era where personalized medicine is the ultimate goal. This complexity, however, makes even the more remarkable the fact that crude routine blood tests, such as the NLR, can demonstrate, in at least eight studies now [17–24], such powerful prognostic ability in liver transplantation for HCC. While we are waiting for tumor immunologists to unravel all the secrets of the immune system, there may just be time for patients to benefit from the cheap and easily accessible information available from a routine blood draw.

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