NARRATIVE REVIEW

Inflammatory mediators as surrogates of malignancy

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Abstract

Inflammation related to cancer occurs in the cellular vicinity of the tumour and is involved with predictions related to the course of disease and survival prognosis in varioua malignancies. These inflammatory markers affect different phases of tumourigenesis, i.e. carcinogenesis, tumour expansion, lymphovascular invasion, and distant metastasis, and, as a result, tumour cells can activate immune mediators and cells directly and/or chemokines as well as prostaglandins. Numbers of circulating different blood cells, i.e. lymphocytes, platelets, neutrophils and levels of plasma proteins, like C-reactive protein and interleukins that are components of inflammatory responses, are hallmarks of pathways leading to tumourigenesis. Thus, they can provide vital information in stratifying patients according to the risk and precisely targeted clinical care and outcome in malignancies. The current narrartive review was planned to discuss the role of platelet-to-lymphocyte ratio alongside the use of systemic immune inflammation index as the inflammatory mediators of malignancies along with overview of their role in different studies. It was also planned to recommend what the future studies should should aim at, including multiple risk factors, exposures and inflammatory profiles and as well as their combined interactions, for a better understanding of the role of the inflammatory mediators in malignancy.

Keywords: Immune Markers, Inflammatory markers, Carcinoma, Metastatic Cancer, Cancer Survival.

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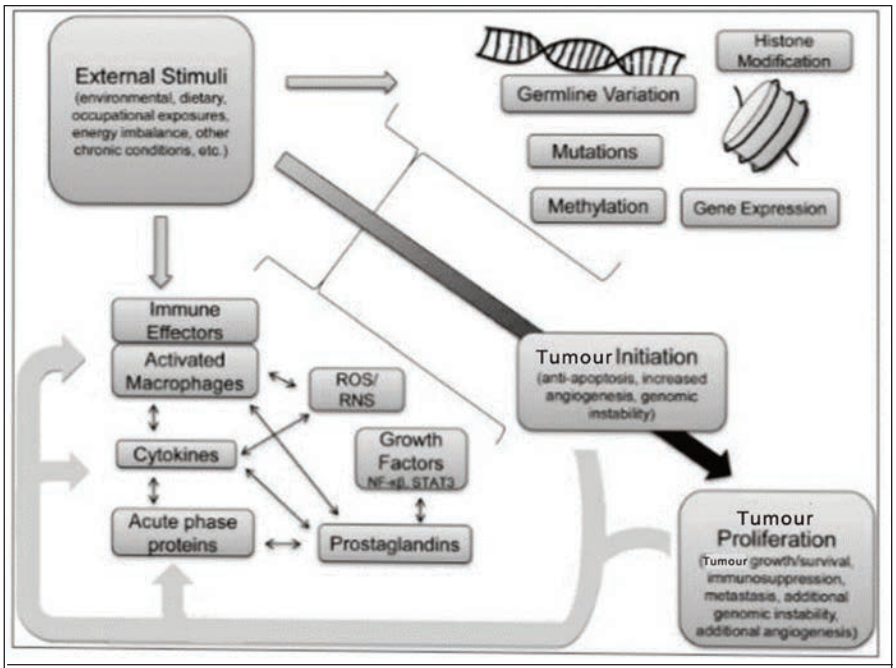

Figure-1: The complex interactions involved in the role of inflammation in the cancer progression spectrum.

Introduction

Inflammation related to cancer occurs in the cellular vicinity of the tumour and has a role in the predictions related to course of the disease and survival prognosis in various malignancies.[1] These inflammatory markers affect different phases of tumourigenesis, i.e. carcinogenesis, tumour expansion, lymphovascular invasion, and distant metastasis, and, as a result, tumourigu cells can activate immune mediators and cells directly and/or chemokines as well as prostaglandins.[2] Numbers of circulating different blood cells. i.e. lymphocytes, platelets, neutrophils and levels of plasma proteins, like C-reactive protein (CRP) and interleukins (ILs) that are components of inflammatory responses, are hallmarks of pathways leading to tumourigenesis (Figure-1). They can provide vital information in stratifying patients according to the risk, and encure precisely-targetted clinical care and outcome in malignancies.[3]

In today's world, early detection and correct disease prognosis are important parts of the management of malignancies. This early disease detection identifies cancer at a stage where it can be curative. The prognostic factors

are predetermined and that makes it easier for patients and doctors to make important decisions, like aggressive therapy or inducing patients to clinical trials.[4] At this time, different modalities that can predict or determine the tissue diagnosis, size of tumour, histopathological grading and type have their limitations and can often mislead the physician. Also, they are not absolute in stratifying patients as high- or low-risk different tumours have their specific immune responses, genetic predispositions and progressions which vary depending upon tumour's feature as well as patient's characteristics. One of the different ways to assess body's immunity status is to measure different kinds of blood cells through the simplest of laboratory tests, like complete blood count (CBC).[5] The most often requested lab investigation, CBC comprises a computerised haemogram and a five-cell digital differential number. Total and differential white blood cell (WBC) count composed of neutrophils, lymphocytes, monocytes, eosinophils and basophils, red blood cells (RBCs), haematocrit, haemoglobin (Hb), RBC indices, like mean corpuscular volume (CPV), mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration, platelet count and mean platelet volume (MPV) are among the cellular readings in a CBC count. Some other peripheral blood measurements can also provide important information on inflammatory markers, like CRP. These immune components when combined may have the ability to predict prognosis in malignancies. When contrasted to more aggressive conventional testing and staging tests, such as tumour volume, histological grade, vascularity and lymph node (LN) malignancies, which would necessitate surgery or costly imaging modalities, a CBC is affordable and can be conducted on a daily basis with negligible harm to patients.

There is a vast amount of evidence in literature that highlights the use of routine blood tests in determining prognosis and treatment of patients with malignancies. A recent research showed that tumour management through immunotherapy is possible with the help of peripheral immunoreactive blood components[6] and another research showed that activation of peripheral immune system can predict the recovery time after surgery.[7] According to the literature, different types of tumours show the relative number of platelets and neutrophils in relation to lymphocytes, and this appears to be a better predictive measure compared to each of these components independently. There are several grading methods, such as the Glasgow Prognostic Score (GPS), which considers inflammatory processes by quantifying CRP and serum albumin and is extremely efficient in predicting overall survival (OS) rates in many solid visceral cancers. The current narrative review was planned to look at neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and CRP to evaluate their efficacy in terms of malignancy management and survival.

Platelet-to-lymphocyte ratio (PLR)

The relative number of platelets to lymphocytes, which is known as PLR, is thought to have roles that can affect the growth and progression of cancer in systemic circulation. Platelets release metalloproteinases that cause tumour cells to leave their site of division and extravasate toward other structures.[8] Platelets also cause neovascularisation by releasing the angiogenic factors and they can supply nutrients to the tumour cells.[9] Platelets not only enhance the tumour growth and progression, but also sustain their growth and can combat against the killer T cell-mediated cellular destruction circulating in the blood[10] In short, cancerous cells develop a symbiotic relationship in which they cause platelet counts to enhance and cause activation by the release of various thrombocytopenic cytokines and platelet agonists.[11]

Two types of lymphocytes are present in systemic circulation, i.e. T cells that destroy cancerous cells and virus-infected host cells, and B cells that produce antibodies which are an effective part of the body's defense against bacteria, viruses and toxins. So these cell lineages of lymphocytes have a critical role in the body's defence against cancerous cells by inducing cell death and hampering tumour's growth.[10]

PLR has shown to be able to assess the tumour's presence, its progression and response to different drug treatment of malignancies.[12] A meta-analysis of 18 studies with 2453 ovarian cancer patients showed that PLR was a reliable marker in predicting the disease staging and its response to chemotherapy with accuracy of 55-80%[13] (Figure-2). This sharp variation is due to variations in choosing the PLR cut-off value. Some initial studies found PLR cut-off to be 144.3 but their sensitivity and specificity were low at 54% and 59%.[14] Later, Bakacak et al. raised the cutoff to 161.13 with specificity and sensitivity of 81.8% and 50.8% respectively.[15]

Raised PLR levels are an important factor for bad prognosis in determining OS in gastric, colorectal, ovarian, hepatocellular and lung cancers.[16] Cases with PLRs <200 had a higher chance of surviving (progression-free survival [PFS] p=0.003; OS p=0.002).[17] Nevertheless, the relevance of PLR in forecasting outcome is still debatable, as it has struggled to help determine OS in a number of other studies.[18-20] Xu et al. conducted a meta-analysis of PLR in individuals with stomach cancer. The PLR was associated with an increased risk of lymphadenopathy (odds ratio [OR] 1.5, 95% confidence interval [CI]: 1.24-1.82) and raised the

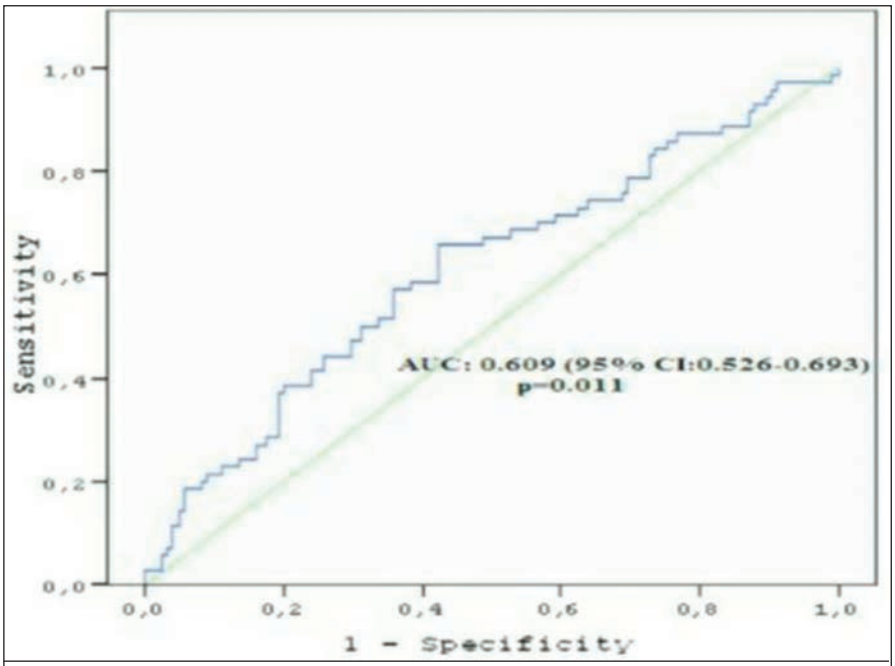

Figure-2: Receiver operating characteristic (ROC) curve analysis for platelet-to-lymphocyte ratio (PLR) in the prediction of adolescent ovarian neoplasms.

risks of advanced stage malignancy (OR 1.99, 95% CI: 1.60-2.46), confirming that it would not be a true indicator of OS.[20]

Systemic immune-inflammation (SII) index

Hu et al.[21] were the first to define the systemic immune-inflammation (SII) index based on the total counts of neutrophil, lymphocyte and platelet. It is not quite clear that high SII leads to a poor prognosis in patients who have solid organ cancer. Several potential mechanisms have been said to explain the prognostic values of SII. It is believed that neutrophils expand both in the tumour microenvironment and in systemic circulation, and in general lead to poor prognosis in patients with solid organ cancers.[22] Neutrophils can activate the endothelial lining of the blood vessels and parenchymal cells to increase adhesion of tumour cells that are in circulation and lead to distant metastasis.[23] Increased amount of neutrophills in blood is actually an inflammatory reaction which suppresses the cytolytic function of immune system, such as lymphocytes, activated T cells, and natural killer cells, therefore inhibiting the immune system. Secondly, platelets can function as "cloaks" for circulatory tumour cells (CTCs), protecting them from immune system destruction.[24] Platelet and endothelial cell adhesive proteins may potentially contribute to dissemination by increasing tumour cell efflux[24] Thirdly, the significance of lymphocytes has been underlined in numerous studies in which increased tumour-infiltrating lymphocytes (TILs) have been linked to improved response to cytotoxic therapy and survival in people with cancer.[25]

Several studies have shown that SII can determine prognosis for malignancies to much precise extent compared to the single-variable indices, such as the (PLR and the NLR.[26-28] Chen et al. were the ones who first showed that SII had a better predictive power compared to the NLR and PLR in cases with colorectal cancer following surgical intervention.[29] Following that, Passardi et al. and Yang et al. validated SII's predictive usefulness.[30,31]These investigations[30] were, however, hampered by a lack of information on pathological characteristics and treatment regimens. In the case of metastatic colorectal cancer (mCRC), variables such as metastasectomy, adjuvant treatment, and metastatic locations, may confuse survival analyses.[32] As a result, the independent impact of SII to longevity in the setting of recognised prognostic variables in mCRC remains unknown.[33] To date, research has focussed on local lymphocytic reactions or systemic inflammatory responses in isolation; nevertheless, the connection between local immunological state and the systemic milieu in mCRC individuals is also of relevance.[34] As a result, the current study investigated the SII's predictive power in mCRC, whether it has been linked with TILs, and how these variables might be coupled to accurately assess combined survival chances.[35]

Integrative approach and future research

It has been shown in various completed and ongoing studies that inflammatory markers have an important role in tumour development and progression, and different approaches to determine the roles of immune-targeted therapy and risk profiles have been advised. Also, therapies directed towards any single marker will not be useful and they will not be effective in reducing the tumour burden. It is, therefore, recommended that future research should aim at studying multiple risk factors, exposures and inflammatory profiles and their combined interactions. Also, genetic makeup, hereditary transmissions, and gene expression behaviours must be a part of profiling with the target to develop a complete image and its associations. This requires studies at a large scale that will need funding and bio-profiles of the population.

Second, data in the available studies should be used to

create a complete integrative hypothesis and to ascertain the causalities. This demands the complete analysis of all the scattered data and their correlation with future research. Also, it will help in determining the links between lifestyles and genetic makeup of inflammatory markers of interest for the population in which behaviours and patterns are to be studied. To fully untangle the complicated relationships of relevance, mediating studies or structural equation investigations are required.

Third, if practicable, causal and prognostic relationships should be explored across tumour tissues. Imbalance in the indicators of modified inflammation have been linked to malignancies at various locations, but it is apparent that inflammatory abnormalities play an important role to some extent in most of the solid target tissues. When sample availability allows, for example, in a large cohort context, thoroughly examining relationships equally across cancer locations substantially improves the potential value of discovering chemopreventive or curative targets. Several projects are ongoing to promote this idea of cross-cancer inflammation, but additional studies are required.

Finally, from the standpoint of secondary prevention, numerous research groups have evaluated and continue to assess the value of inflammatory biomarkers in the creation of risk prediction models. The Prostate, Lung, Colorectal and Ovarian (PLCO) cancer research discovered that smokers with increased CRP and IL-8 had the greatest 10-year projected risk for lung carcinoma.[36]

Conclusion

Extensions of the above mentioned approaches and models to additional types of inflammatory markers and cancer locations may aid in identifying people at highest risk of getting cancer, and, as a result, refine the group that would profit most from enhanced clinical settings on their inflammatory characteristics.

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