EDITORIAL

Emerging role of eosinophils in immune-related adverse events related to therapy with immune checkpoint inhibitors

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Eosinophils are a subset of granulocytic leukocytes that are not only formed components of the blood, but also cells residing in the lung, breast, gastrointestinal tract, and reproductive organs.[1] Eosinophils are produced in the bone marrow from pluripotent stem cells and their life cycle also includes blood and tissue phases. Some cytokines (interleukin [IL] 3, IL-5, granulocyte-macrophage colony-stimulating factor) play a key role in eosinophil proliferation and differentiation.[2] The pathophysiological functions of eosinophils are related to the degranulation of cytoplasmic granules that contain peroxidase, cationic proteins, eosinophil-derived neurotoxin, and major basic protein.[3] Eosinophils can also secrete several cytokines and soluble factors that may have either antitumor effects or they may stimulate tumor progression.[1] Additionally, eosinophils are involved in the polarization of T cells to either the Th2 or Th1 pathway,[4] whereas T cells regulate eosinophils through specific pathways involving Th2 cytokines such as IL-5 (regulating eosinophil expansion in the bone marrow and blood) and IL-13 (regulating eotaxin production).[2]

The eosinophil has long been linked to innate mucosal immunity; it is a prominent cell type in host defense (particularly against helminths) and represents an essential component of allergic inflammation.[5] Eosinophils are also involved in human pathophysiology in certain systemic diseases characterized by blood eosinophilia (which is uncommon in healthy individuals) accompanied by eosinophilic tissue infiltration.[6] However, eosinophils are increasingly involved in other pathophysiological processes and diseases based on their capacity to release cytokines into the local environment.[3] These processes include tissue remodeling during puberty and pregnancy, reorganization of adipose tissue, and neoplasm surveillance.[6]

Although eosinophils were identified in patients with neoplasia more than 120 years ago, their precise pathogenic role in cancer is still not well characterized. Recent data suggest that eosinophils may show regulatory functions towards other immune cells residing in the tumor microenvironment (TME) and may also display direct cytotoxic functions against malignant cells,[7] leading to a paradoxical role of these cells that could have either antitumor or protumor effects, depending on different underlying factors present in the TME.[8] On one hand, eosinophils may regulate tumor progression, either directly by interacting with tumor cells or indirectly by influencing the TME-residing immune cells; in response to diverse stimuli, eosinophils synthesize and secrete a wide range of molecules, including cationic proteins, that can potentially kill tumor cells. On the other hand, eosinophils can also secrete proangiogenic and matrix-remodeling soluble mediators that could promote tumor growth.[9]

The identification of an excess of eosinophils both in the tumor tissue (tumor-associated tissue eosinophilia) and in the peripheral blood (eosinophilia) has been frequently associated with better outcomes in most, but not all, neoplasias.[8] While eosinophilic infiltration is considered an unfavorable prognostic marker in patients with Hodgkin lymphoma, it has been linked to a favorable prognosis in patients with solid cancer, including colorectal, breast, or prostate cancer.[1]

With the progressive use of cancer immunotherapies, eosinophil count has also been identified as a potential predictive marker for a beneficial clinical response to immune checkpoint inhibitors (ICPIs) in patients with metastatic melanoma treated with pembrolizumab[8] or in those

TABLE 1 Eosinophilic immune-related adverse events reported following therapy with immune checkpoint inhibitors

Blood count	Eosinophilia
	Hypereosinophilia (absolute eosinophil count >1500/μl)
Skin and soft tissues	Eosinophilic fascitis
	DRESS
	Eosinophilic lichen
	Eosinophilic folliculitis
	Eosinophilic maculopapular rash
	Eosinophilic psoriasiform rash
	Eczematiform dermatitis
	Eosinophilic bullous pemphigoid-like eruption
Respiratory	Eosinophilic pneumonia
	Eosinophilic bronchiolitis
	Eosinophilic rhinosinusitis
Digestive	Eosinophilic enteritis
	Eosinophilic esophagitis
	Eosinophilic cholangitis
Other organ-specific diseases	Eosinophilic myocarditis
	Eosinophilic nephritis
Systemic diseases	EGPA
	Hypereosinophilic syndrome

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; EGPA, eosinophilic granulomatosis with polyangiitis

with classical Hodgkin lymphoma treated with nivolumab.[9] Specifically, a significant increase in the absolute eosinophil count (AEC) has been reported in those patients who responded to combined programmed death receptor 1 inhibition and intratumoral IL-2.[10] Although some authors have suggested that the eosinophilia reported following ICPI therapies could reflect an allergic response triggered by the treatment, experimental data are supporting a potential role of anti-CTLA-4 therapies in favoring intratumoral eosinophil accumulation mediated by $CD4^+$ and $CD8^+$ T cells expressing IL-5, CCL5, CCL11, and interferon γ.[9]

In the current issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Osawa et al[11] reported that in patients with non–small cell lung cancer treated with ICPI monotherapy, peripheral eosinophilia (defined as either an eosinophil percentage ≥5% or an eosinophil count ≥330/μl) within 6 weeks after the initiation of treatment was a significant favorable prognostic factor. These results confirmed similar findings reported in patients treated with ICPI therapy for melanoma, urothelial cancer, neck squamous cancer, or Hodgkin lymphoma. However, in the multivariate analysis carried out by the authors[11] an additional striking association with eosinophilia was found. Those patients presenting eosinophilia within 6 weeks after starting ICPI therapy had a nearly 3-fold higher risk of developing immune-related adverse events (irAEs), excluding those requiring ICPI discontinuation. The role of eosinophilia in ICPI-related irAEs is being increasingly investigated. On one hand, there is a long list of eosinophilic irAEs triggered by ICPI therapy (**TABLE 1**), including both organ-specific and systemic diseases. A recent study has identified 37 cases of moderate-to-severe eosinophilia induced by ICPIs, with a median AEC of 2.7 G/l and eosinophil-related clinical manifestations were reported in 21 cases (57%).[12] Additional studies have reported that irAEs are more common in patients with peripheral eosinophilia, and that eosinophilia is significantly associated with cutaneous irAEs, with patients with any type of cutaneous irAE having a better overall survival.[13] Phillips et al[14] reported that eosinophil-related cutaneous irAEs were recorded in 13 (5%) of 273 patients, and mainly involved rash and pruritus. Eosinophilia and serum levels of immunoglobulin E were associated with severe irAEs (grade 3 or greater). Eosinophilia has also been related to pulmonary irAEs. Chu et al[15] reported that among patients with non–small cell lung cancer receiving ICPIs, a baseline high AEC was associated not only with an increased risk of ICPI-related pneumonitis, but also with a better clinical outcome.

In summary, recent studies have identified an emerging role of eosinophils in patients with cancer treated with ICPI therapy. Eosinophilia has been consistently reported as a favorable prognostic marker of cancer outcomes; at the same time, it is closely associated with irAEs, especially those involving the skin and lungs. A routine eosinophil count assessment should be considered as a simple and useful test to be carried out in patients with cancer before receiving immunotherapy.

ARTICLE INFORMATION

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