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Current Review

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Eosinophil-mediated inflammation in the absence of eosinophilia

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ABSTRACT

The increase of eosinophil levels is a hallmark of type-2 inflammation. Blood eosinophil counts act as a convenient biomarker for asthma phenotyping and the selection of biologics, and they are even used as a prognostic factor for severe coronavirus disease 2019. However, the circulating eosinophil count does not always reflect tissue eosinophilia and vice versa. The mismatch of blood and tissue eosinophilia can be seen in various clinical settings. For example, blood eosinophil levels in patients with acute eosinophilic pneumonia are often within normal range despite the marked symptoms and increased number of eosinophils in bronchoalveolar lavage fluid. Histological studies using immunostaining for eosinophil granule proteins have revealed the extracellular deposition of granule proteins coincident with pathological conditions, even in the absence of a significant eosinophil infiltrate. The marked deposition of eosinophil granule proteins in tissue is often associated with cytolytic degranulation. Recent studies have indicated that extracellular trap cell death (ETosis) is a major mechanism of cytolysis. Cytolytic ETosis is a total cell degranulation in which cytoplasmic and nuclear contents, including DNA and histones that act as alarmins, are also released. In the present review, eosinophil-mediated inflammation in such mismatch conditions is discussed.

Keywords: Eosinophil granule proteins; Eosinophils; Extracellular traps

INTRODUCTION

Allergy, a hypersensitivity reaction initiated by specific immunologic mechanisms [1], is often associated with tissue eosinophilia [2]. In addition, eosinophil accumulation is also associated with malignancy, infection, and various homeostatic conditions. For example, eosinophils home into the uterus, which is regulated by the estrus cycle [3, 4]. Eosinophils in the blood can be readily counted. Although these cells form a minor (<5%) component of the circulating leukocyte population in the blood, larger numbers of tissue-dwelling eosinophils are present outside of the vasculature [5]. Nevertheless, the blood eosinophil count is an easy-to-access biomarker for various clinical applications. For asthma phenotyping and the

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Conflict of interest

MF received grant support from GlaxoSmithKline Japan Research Grants 2018; PA has received research support and consultancy fees from and has been on advisory boards for AstraZeneca and GlaxoSmithKline; SU received honoraria for lectures from AstraZeneca and GlaxoSmithKline as well as grant support from AstraZeneca, Novartis, and Maruho. The rest of the authors have no conflicts of interest.

Author Contributions

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selection of biologics, the blood eosinophil count is the best-established biomarker [6]. In patients with severe chronic obstructive diseases, blood eosinophil counts are associated with the risk of exacerbations and the benefit of inhaled corticosteroid use [7]. A lower blood eosinophil count is also useful as a poor prognostic factor for severe coronavirus disease 2019 (COVID-19) [8, 9].

Eosinophils develop in the bone marrow and are released into blood circulation once they are maturated. Circulating eosinophils can subsequently transmigrate into the gastrointestinal tract, lungs, adipose tissue, thymus, spleen, lymph nodes, and mammary glands, where they exert various essential homeostatic functions [10, 11]. The life span of eosinophils is unclear, but it has been estimated to be less than 1 week under homeostatic conditions [12]. The tissue presence of eosinophils is determined by their recruitment, retention, and clearance [13]. Therefore, tissue eosinophilia can be caused by increased migration, prolonged survival, impaired phagocytic clearance, or decreased luminal entry [14].

The activation status of eosinophils is mainly tuned by receptors expressed on their cell surfaces. As a short-lived, nondividing cell, eosinophil “activation” has been recognized as the release of bioactive mediators into the extracellular milieu [15]. This is in contrast to lymphocytes, for which “activation” usually means proliferation and clonal expansion of antigen-specific lymphocytes [16]. The multifaceted role of eosinophils is evidenced by their range of cell densities and cell-derived mediators.

SECRETORY MECHANISMS OF EOSINOPHILS

Because eosinophils are a rich source of bioactive mediators, the simplified hypothesis is that the amount of eosinophil-derived inflammatory mediators in the microenvironment is the primary cause of eosinophilic inflammation. Eosinophils contain approximately 200 granules per cell [17]. These granules contain 4 major cationic (basic) proteins, that is, major basic protein (MBP), eosinophil-derived neurotoxin (EDN), eosinophil cationic protein (ECP), and eosinophil peroxidase (EPO), which play important roles in eosinophil-mediated inflammation [18]. Granule-stored cytokines in human eosinophils are released by 3 secretory processes: classical exocytosis, piecemeal degranulation, and cytolysis/extracellular trap cell death (ETosis) [5, 19].

Classical exocytosis is a granule secretory system in which intracellular granules fuse with the plasma membrane and release their entire contents extracellularly via a secretory pore. This mechanism is not usually observed *in vivo*. In compound exocytosis, granules fuse to each other, forming large channels within the cytoplasm, and the cells then secrete the entire intragranular contents of multiple granules [18].

Piecemeal degranulation is thought to be the main degranulation process used by eosinophils. In piecemeal degranulation, the granule contents are selectively mobilized into small round vesicles and tubular structures termed eosinophil sombrero vesicles. The tubular eosinophil sombrero vesicles express cytokine receptor chains that are bound by cytokine ligands, such as interleukin (IL)-4 [5]. These vesicles become fused with the plasma membrane and release their granule-derived contents into extracellular spaces [20, 21]. Ultrastructure of exocytosis and piecemeal degranulation show an emptying of the secretory granules or lucent areas in the core of intact eosinophils [18].

Cytolysis or ETosis is a recently recognized type of programmed cell death that is characterized by the dissolution of nuclear and plasma membranes and release of chromatin fiber called an extracellular trap [22-24]. In eosinophils, ETosis-derived cell-free extracellular granules express functional receptors on their membranes [18, 19, 25, 26]. Upon activation by ligand stimulation, the granules release their contents, which include EDN [27, 28]. Eosinophil ETosis (EETosis) is considered to contribute to the sterilization and trapping of pathogens by extracellular traps, granule proteins, and nuclear-derived components, all of which have cytotoxicity [29, 30].

BIOACTIVE MEDIATORS OF EOSINOPHILS

The functions of the major mediators derived from human eosinophils are summarized in **Table 1**. MBP is localized in the core of specific granules, while EDN, ECP, and EPO are localized in the matrix of specific granules [31-33]. Although all 4 of these granule proteins have toxicity for helminth parasites [34], each has various biological activities in addition to its antimicrobial activity. MBP-2 and EPO are distributed only in eosinophils [35, 36], whereas the other granule proteins are found in additional cells and tissues [37-39].

Table 1. Eosinophil-derived mediators

Eosinophil	Mediators	Cell distribution	Functions	Selected references
Eosinophil-specific	MBP1/2	Granule core	Toxic to cells and tissues	Gleich GJ, et al. J Immunol 1979;123:2925–7. [46]
			Toxic to helminth parasites	Hamann KJ, et al. J Immunol 1990;144:3166–73. [34]
				Butterworth AE, et al. J Immunol 1979;122:221–9. [162]
			Toxic to bacteria	Lehrer RI, et al. J Immunol 1989;142:4428–34. [41]
			Disrupts the lipid bilayer membrane	Gleich GJ, et al. Annu Rev Med 1993;44:85–101. [163]
			Inhibits the Muscaline 2 receptor	Jacoby DB, et al. J Clin Invest 1993;91:1314–8. [49]
			Induces mediator release from basophils and mast cells	O'Donnell MC, et al. J Exp Med 1983;157:1981–91. [42]
				Fujisawa D, et al. J Allergy Clin Immunol 2014;134:622–33.e9. [43]
				Zheutlin LM, et al. Int Arch Allergy Appl Immunol 1985;77:216–7. [164]
			Induces IL-8 production from eosinophils	Kita H, et al. J Immunol 1995;154:4749–58. [45]
			Induces detachment of tracheal epithelial cells	Hastie AT, et al. Am Rev Respir Dis 1987;135:848–53. [47]
			Induces cessation of ciliary activity	
			Induces platelet activation	Rohrbach MS, et al. J Exp Med 1990;172:1271–4. [44]
			Induces amyloid deposition	Soragni A, et al. Mol Cell 2015;57:1011–21. [165]
	EDN	Granule matrix	Toxic to helminth parasites	Hamann KJ, et al. J Immunol 1990;144:3166–73. [34]
			Has RNase2 activity	Slifman NR, et al. J Immunol 1986;137:2913–7. [166]
			Induces the Gordon phenomenon	Fredens K, et al. J Allergy Clin Immunol 1982;70:361–6. [167]
			Induces dendritic cell activation	Yang D, et al. J Exp Med 2008;205:79–90. [57]
			Induces MMP9 expression and apoptosis in keratinocytes	Amber KT, et al. Exp Dermatol 2018;27:1322–7. [67]
	ECP	Granule matrix	Has RNase3 activity	Gullberg U, et al. Biochem Biophys Res Commun 1986;139:1239–42. [61]
				Slifman NR, et al. J Immunol 1986;137:2913–7. [166]
			Induces the Gordon phenomenon	Fredens K, et al. J Allergy Clin Immunol 1982;70:361–6. [167]
			Toxic to helminth parasites	McLaren DJ, et al. Parasite Immunol 1981;3:359–73. [62]
				Hamann KJ, et al. J Parasitol 1987;73:523–9. [54]
			Cytotoxic	Rosenberg HF and Dyer KD. J Biol Chem 1995;270:7876–81. [168]
			Toxic to bacteria	Lehrer RI, et al. J Immunol 1989;142:4428–34. [41]
			Induces amyloid-like aggregation	Torrent M, et al. PLoS Pathogens 2012;8:e1003005. [56]
			Induces mediator release from basophils and mast cells	Zheutlin LM, et al. Int Arch Allergy Appl Immunol 1985;77:216–7. [164]
			Inhibits TNF-α production by human macrophages	Pulido D, et al. FEBS J 2016;283:4176–91. [60]
			Induces MMP9 expression and apoptosis in keratinocytes	Amber KT, et al. Exp Dermatol 2018;27:1322–7. [67]
			Induces plasminogen activation	
			Enhances factor XII-dependent reactions	Dahl R and Venge P. Thromb Res 1979;14:599–608. [65]
				Venge P, et al. Thromb Res 1979;14:641–9. [64]

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Table 1. (Continued) Eosinophil-derived mediators

Eosinophil	Mediators	Cell distribution	Functions	Selected references
	EPO	Granule matrix	Toxic to helminth parasites	Hamann KJ, et al. J Immunol 1990;144:3166–73. [34]
			Toxic to bacteria	Migler R, et al. Blood 1978;51:445–56. [75]
				Wang JG, et al. Blood 2006;107:558–65. [77]
			Toxic to tumor cells	Jong EC and Klebanoff SJ. J Immunol 1980;124:1949–53. [76]
			Induces tissue factor and thrombosis	Wang JG, et al. Blood 2006;107:558–65. [77]
			Binds to the surface of microorganisms and enbhances phagocytosis	Ramsey PG, et al. J Immunol 1982;128:415–20. [78]
			Mediates mucus plugging of the airways	Dunican EM, et al. J Clin Invest 2018;128:3:997–1009 [79]
			Inactivates of leukotrienes	Henderson WR, et al. J Immunol 1982;128:2609–13. [81]
			Induces histamine release from mast cells	Henderson WR, et al. J Exp Med 1980;152:265–79. [80]
				Fujisawa D, et al. J Allergy Clin Immunol 2014;134:622–33.e9 [43].
	Galectin-10	Peripheral cytoplasm	Forms Charcot-Leyden crystals	Ueki S, et al. Blood 2018;132:2183–7. [84]
			Promotes allergic inflammation	Persson EK, et al. Science 2019;364:4295. [85]
			Regulates the proliferative capacity and suppressive function of CD25+ Treg cells	Kubach J, et al. Blood 2007;1;110:1550–8. [169]
			Involved in the secretory response via lysophospholipase activity	Weller PF, et al. J Leukoc Biol. 2020;108:105–12. [87]
			Induces granuleogenesis and vesicular transport of granule proteins	Grozdanovic MM, et al. J Allergy Clin Immunol 2020;146:377–89.e10. [88]
Nonspecific for eosinophil	Histones	Nucleus	Promotes apoptosis	Barrero CA, et al. Am J Respir Crit Care Med 2013;188:673–83. [91]
				Gilthorpe JD, et al. F1000Res 2013;2:148. [92]
			Stimulates neurogenesis	Mishra B, et al. J Neurosci 2010;30:12400–13. [170]
			Regulates macrophage migration and endocytosis	Brix K, et al. J Clin Invest 1998;102:283–93. [171]
			Regulates neutrophil migration	Xu J, et al. Nat Med 2009;15:1318–21. (in mice) [172]
			Cytotoxic to endothelial cells	Bosmann M, et al. Faseb J 2013;27:5010–21. [173]
				Allam R, et al. J Am Soc Nephrol 2012;23:1375–88. [174]
			Toxic to bacteria	Hirsch JG. J Exp Med 1958;108:925–44. [90]
			Stimulates TLR signaling pathways	Huang H, et al. Hepatology 2011;2:54:999–1008. [93]
				Semeraro F, et al. Blood 2011;118:1952–61. [95]
				Kawano H, et al. Lab Invest 2014;94:569–85. [94]
			Induces NLRP3 Inflammasome activation	Allam R, et al. Eur J Immunol 2013;43:3336–42. [96]
				Huang H, et al. J Immunol 2013;191:2665–79. [97]
			Promotes thorombin generation	Fuchs TA, et al. Blood 2011;118:3708–14. (in mice) [98]
				Ammollo CT, et al. J Thromb Haemost 2011;9:1795–1803. [99]
			Induces platelet aggregation	Lam FW, et al. Thromb Res 2013;132:69–76. [101]
				Carestia A,et al. Thromb Haemost 2013;110:1035–45. [100]
	dsDNA	Nucleus	Contributes to microbial pathogen containment	Kaplan MJ and Radic M. J Immunol 2012;189:2689–95. [89]
			Stimulates autoimmune responses	Garcia-Romo GS, et al. Sci Transl Med 2011;3:73ra20. [104]
				Kessenbrock K, et al. Nat Med 2009;15:623–25. [105]
				Hakkim A, et al. Proc Natl Acad Sci USA 2010;107:9813–8. [175]
				Lande R, et al. Sci Transl 2011;Med3:73ra1. [106]
			Induces vascular damage	Villanueva E, et al. J Immunol 2011;187: 538–52. [102]
				Gupta AK, et al. FEBS Lett 2010;584:3193–3. [103]
			Promotes thorombosis	Fuchs TA, et al. Proc Natl Acad Sci USA 2010;107:15880–5. [176]

MBP1/2, major basic protein 1/2; IL-8, interleukin-8; EDN, eosinophil-derived neurotoxin; MMP9, matrix metallopeptidase 9; ECP, eosinophil cationic protein; TNF, tumor necrosis factor; EPO, eosinophil peroxidase; TLR, Toll-like receptor; dsDNA, double-stranded DNA.

Nevertheless, these granule proteins characterize eosinophil-mediated inflammation with their abundance.

Major basic protein

There are 2 types of MBP: MBP-1 and MBP-2. MBP-1 is more potent and more widespread compared with its homologue MBP-2, which is only present in eosinophils [35]. MBP is rich in arginine and has strong basicity [40]. It mediates cytotoxicity for bacteria by increasing the permeability of cell membranes [41]. Both MBP and EPO induce histamine release from basophils and mast cells, and histamine release in mast cells occurs through the Mas-related

gene X2 receptor [42, 43]. MBP is also known to be involved in the activation of neutrophils and platelets [44] and to induce IL-8 production by eosinophils themselves [45]. According to an *in vitro* study, MBP causes damage to various cells and tissues, such as the intestine, spleen, skin, and tracheal epithelium [46]. Furthermore, MBP induces the detachment of airway epithelium and arrest of ciliary activity, which may be related to the pathogenesis of severe asthma [47]. MBP-stimulated normal human bronchial epithelial cells have elevated expression levels of endothelin-1, transforming growth factor (TGF)-α, TGF-β, platelet-derived growth factor, matrix metallopeptidase 9, and fibronectin, which suggests that MBP affects the composition of the extracellular matrix and turnover of airway epithelium [48]. MBP was also suggested to enhance bronchoconstriction in asthma through blocking muscarinic M2 receptors, followed by eliminating the negative feedback and increasing the release of acetylcholine [49].

Eosinophil-derived neurotoxin

The RNase superfamily member EDN, encoded in humans by the gene *RNASE2*, is the second-most abundant protein in the human eosinophil proteome out of the 7,086 proteins identified by proteomics of peripheral blood eosinophils [50]. EDN can be isolated not only from eosinophils but also from neutrophils as well as the liver, spleen, kidney, and urine [38, 51-53]. In neutrophils, EDN is present in the neutrophilic granules, as demonstrated by immunoelectron microscopy [38]. EDN has limited toxicity for helminth parasites compared with MBP and ECP [34, 54], but this protein is active against RNA viruses. Additionally, EDN is 100-fold more ribonucleolytically active compared with ECP [55]. Intrathecal injection of EDN or ECP into rabbits causes the death of cerebellar Purkinje fibers, which is known as the Gordon phenomenon [56]. A recent report has shown that EDN can act as an alarmin, is involved in the activation of dendritic cells through the TLR2–MyD88 signaling pathway, and activates the type-2 immune response [57].

Eosinophil cationic protein

ECP, encoded in humans by the gene *RNASE3*, also belongs to the RNase superfamily. Compared with EDN, ECP is more cationic and more toxic to bacteria [58]. ECP can destabilize bacterial lipid bilayers and neutralize bacterial lipopolysaccharide, which contribute to the toxicity of ECP to bacteria [59, 60]. However, ECP has 125 times lower RNase activity compared with EDN [61]. Regarding the toxicity of ECP to *Schistosoma mansoni*, electron microscopy observation revealed that in ECP-treated *S. mansoni*, blebs were formed on the surface of the parasite and the surface of the parasite was ruptured [62]. The toxicity to helminth parasites of ECP is equivalent to the effect of MBP, but the effect of ECP is slower than that of MBP [54]. Like MBP, ECP mediates histamine release in basophils and mast cells [63]. ECP increases the activation of kallikrein, enhances factor XII, and shortens the blood coagulation time [64]. ECP is also involved in fibrinolysis via plasminogen enhancement [65]. Additionally, ECP inhibits microbial activity by forming amyloid-like aggregates on bacterial surfaces [66]. In a recent report, ECP and EDN both induced the expression of matrix metalloproteinase 9 in keratinocytes and triggered keratinocyte apoptosis, which suggests their potential as therapeutic targets for bullous pemphigoid [67].

Eosinophil peroxidase

EPO is highly cationic, heme-containing oxidoreductase that is similar to myeloperoxidase (MPO) in neutrophils [68]. Although EPO and MPO have 68.3% of the same amino acids [69], there are some differences in their functions; for example, EPO binds to antineutrophil cytoplasmic antibodies and is involved in renal fibrosis [70, 71]. EPO is taken up by

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neutrophils, basophils, and mast cells, and EPO has a higher affinity for neutrophils compared with MPO [72, 73]. By acting as an oxidoreductase, halides are coactivated with reactive oxygen species to produce hypochlorous acid, which is highly toxic to helminth parasites and bacteria [74, 75] as well as toxic to tumor cells [76]. Hypothiocyanous acid (HOSCN) is produced by the oxidation of EPO and induces tissue factor activation, which suggests its involvement in thrombosis. HOSCN also activates the proinflammatory p65/p50 nuclear factor-κB pathway [77]. EPO binds to the surface of microorganisms, thereby facilitating macrophage phagocytosis even in microorganisms that are resistant to macrophage destruction [78]. EPO is associated with mucus plugging of the airways in asthma [79]. Similar to MBP and ECP, EPO induces mast cell degranulation [80]. EPO also inactivates leukotrienes B4, C4, and D4 [81].

Galectin-10 (Charcot-Leyden crystal protein)

Galectin-10 is a cytoplasmic protein that belongs to S-lectin family and the fifth most abundant protein in eosinophils [50]. It was originally recognized as Charcot-Leyden crystal (CLC) protein and later named galectin-10 because of its carbohydrate-binding domain, which is similar to those of other galectin family members. Galectin-10 is expressed predominantly on eosinophils but is also present on macrophages, basophils, and $CD4^+CD25^+$ regulatory T cells [82]. In unstimulated eosinophils, galectin-10 is localized in the peripheral cytoplasm [83]. During the process of EETosis, galectin-10 can redistribute in the cytoplasm and form CLCs intracellularly [84]. EETosis-mediated plasma membrane disintegration causes the extracellular release of galectin-10, resulting in the extracellular formation of CLCs [84]. Recent reports indicate that CLCs promote type-2 immunity [85] and also neutrophilic inflammation [86]. The full function of galectin-10 is still unclear, but reports suggest that this protein regulates the dynamic palmitoylation cycle [87] and is involved in vesicular transport systems and granulogenesis [88].

Histones and double-stranded DNA

EETosis releases eosinophil extracellular traps, which are composed mainly of histones and double-stranded DNA, that is, chromatin fiber. Eosinophil extracellular traps are effective at trapping microbial pathogens because of their net-like structure [89]. A proteome analysis of human eosinophils indicated that histones ranked 3rd, 4th, 6th, and 15th in abundance among the top 15 proteins [50]. The cytotoxic effects to bacteria of histones have been known for more than 50 years [90]. Histones promote cell apoptosis [91, 92] and are involved in inflammation by stimulating Toll-like receptor signaling pathways [93-95] or NLRP3 inflammasomes [96, 97]. Histones have also been recognized as inducers of the blood coagulation system [98-101]. Extracellular double-stranded DNA is known to cause vascular damage [102, 103] and thrombosis, and it can stimulate autoimmune responses, such as systemic lupus erythematosus [104-106].

Other cytokines and lipid mediators

Eosinophils are a rich source of cysteinyl leukotrienes (cysLTs). Leukotriene C4 and its metabolites, leukotriene D4 and leukotriene E4, have varied roles in mediating eosinophilic disorders, including host defense against parasites and allergic inflammation. CysLTs can activate eosinophils in an autocrine manner (they prolong survival), and induce reactive oxygen species production and EDN release from eosinophils [107, 108]. CysLTs are also involved in eosinophil differentiation and maturation in combination with IL-5 [109]. Additionally, extracellular eosinophil granules can release ECP in response to cysLT stimulation via cysLT receptors expressed on the granule membrane [110].

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Eosinophils store a wide array of cytokines, chemokines, and growth factors, including IL-4 [111, 112], granulocyte macrophage colony-stimulating factor (GM-CSF) [113-115], and TGF-β [116-118]. IL-4 induces eosinophil migration into tissues via the expression of adhesion molecule vascular cell adhesion molecule-1 on endothelial cells [119]. Various stimuli, including calcium ionophore [113, 114] and fibronectin [115], can induce GM-CSF production in eosinophils. GM-CSF is involved in the type-2 response in allergic airway inflammation through activating dendritic cells and enhancing eosinophil survival in an autocrine manner [120, 121].

PERIPHERAL VERSUS TISSUE EOSINOPHILIA: LESSONS FROM ACUTE EOSINOPHILIC PNEUMONIA

Peripheral blood eosinophilia can assist in the diagnosis of eosinophilic inflammatory diseases, including eosinophilic pneumonia. Unlike the diagnostic criteria for chronic eosinophilic pneumonia with peripheral blood eosinophilia, the diagnostic criteria for acute eosinophilic pneumonia (AEP) do not require peripheral blood eosinophilia [122]. AEP is caused mainly by inhalational exposure, such as cigarette smoke, including electronic cigarettes or heated tobacco [123], and develops acutely along with respiratory failure. Peripheral blood eosinophilia may be absent at the onset of AEP, especially in smoking-related AEP [124].

We experienced a case in which bacterial pneumonia was suspected because of the patient's neutrophilia, and the results of a bronchoalveolar lavage led to the diagnosis of AEP. A 21-year-old woman had fever and dyspnea 1 week after smoking initiation. Upon hospitalization, she was febrile (39.6°C) and tachypneic with a reduced peripheral oxygen saturation (91%). Her arterial blood gases under room air were: pH, 7.44; PaO_2, 55 mmHg; and $PaCO_2$, 30 mmHg. Her chest x-ray showed bilateral ground grass attenuations mixed with consolidations and a slight pleural effusion.

The laboratory test revealed a white blood cell count of 23,400 cells/μL with neutrophilia (95.8%, 22,417 cells/μL). Her serum C-reactive protein level was 8.2 mg/dL (normal, <0.3 mg/dL), IL-5 level was 1,012 pg/mL (normal, <3.9 pg/mL), and ECP level was 68.9 μg/L (normal, <14.9 μg/L), and her peripheral blood eosinophil count was only 94 cells/μL. Conversely, a marked elevation of eosinophils was observed in her bronchoalveolar lavage fluid (71% eosinophils in the differential cell count), leading to the diagnosis of AEP. A single administration of methylprednisolone (40 mg) and the cessation of cigarette smoking dramatically improved the symptoms of AEP. Notably, in parallel with the patient's improvement of bilateral pulmonary infiltration, her peripheral eosinophil counts reached up to 1,250 cells/μL on day 9 (6 days after methylprednisolone administration) (**Fig. 1A**, **B**).

Before or during eosinophil movement, a cellular shape change related to migration is necessary [2]. We conducted an *ex vivo* eosinophil shape change assay by using flow cytometric measurement of autofluorescence/forward scatter on cells stimulated with cigarette smoke extract [125]. A clear shape change was induced in the patient's eosinophils at the onset, and such changes were not reproduced in cells taken from the patient after the resolution of AEP or in eosinophils from a normal donor (**Fig. 1C**). Thus, it can be speculated that eosinophils have the potential to accumulate in the lung at the onset of AEP.

IL-5 plays a critical role in an eosinophilopoiesis, chemokinesis/chemotaxis, integrin activation, and survival prolongation via apoptosis inhibition [6]. In our case, the initially

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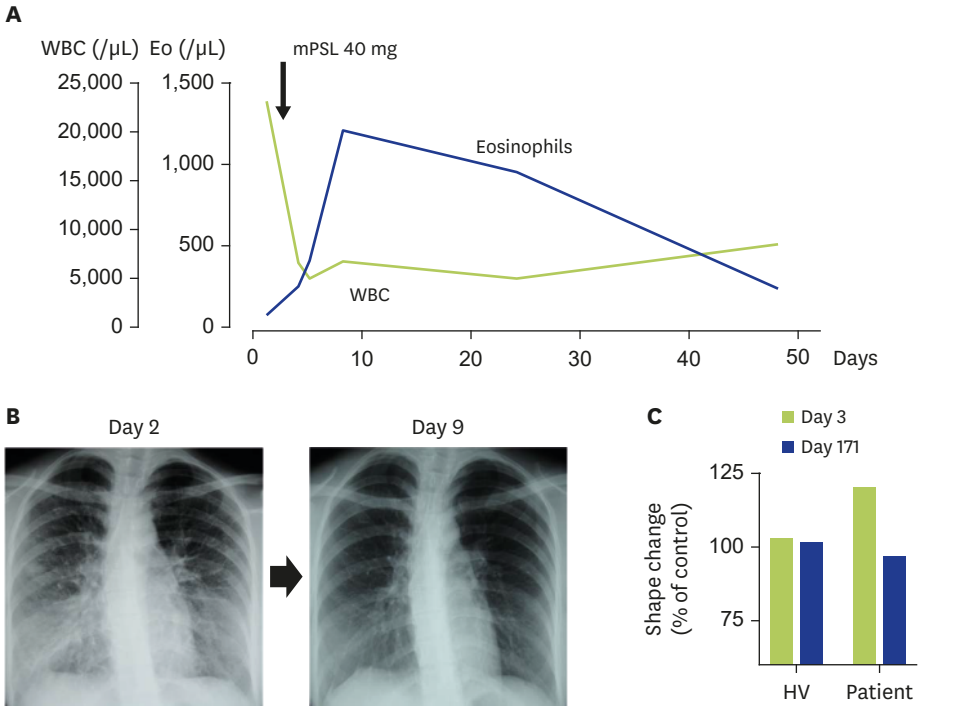

Fig. 1. Clinical course of a case with AEP.
(**A**) Dynamics of blood eosinophil counts. Values indicate the peripheral white blood cell (WBC) counts (green line) and eosinophil (Eo) counts (blue line). On day 2, the patient was treated with an intravenous administration of methylprednisolone (mPSL). (**B**) Chest x-ray on day 2 (before performing a bronchoalveolar lavage and mPSL administration) and day 9 (6 days after treatment). (**C**) Response of eosinophils to cigarette smoke extract (CSE). CSE was prepared as described by a previous report [161]. Peripheral whole blood cells stimulated with CSE for 10 minutes and red blood cells were lysed using BD FACS Lysing Solution (BD Biosciences, San Jose, CA, USA). The eosinophil shape change induced by CSE was evaluated using a FACScan flow cytometer (BD Biosciences). Values shown are the % of control buffer. HV, healthy volunteer.

elevated serum IL-5 level was associated with AEP disease severity, despite the peripheral blood eosinophil counts being in the normal range. Interestingly, serum IL-5 levels have been shown to inversely correlate with peripheral blood eosinophil counts in patients in the initial state of AEP [126]. This is likely caused by the rapid migration of blood eosinophils to the lungs, as illustrated in **Fig. 2A**. Notably, the pathological condition of asthma was recreated in lung-specific IL-5 transgenic mice but not in "systemic" IL-5 transgenic mice [6]. Tissue-specific overproduction of IL-5 might play an important role in the pathogenesis of AEP by recruiting eosinophils from the peripheral blood into the lungs.

In patients with atopic asthma, sputum eosinophil counts and serum IL-5 levels increase after allergen inhalation, whereas blood eosinophil counts decrease for 12 hours [127, 128]. The intravascular residence time of radiolabeled eosinophils in healthy volunteers is approximately 25 hours, although it can be 1.5 hours in a patient with tissue eosinophilic inflammation [129, 130]. Accumulated eosinophils might directly induce eosinophilia through the production of eosinophil chemoattractants, such as leukotriene B4 [131] and C-C chemokine ligand 4 [132]. These data suggest that a dynamic shift of circulating eosinophils into the tissue can occur.

Transient blood eosinophilia after systemic corticosteroid administration is another interesting feature of the present case. This phenomenon has been reported previously;

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Asia Pacific allergy

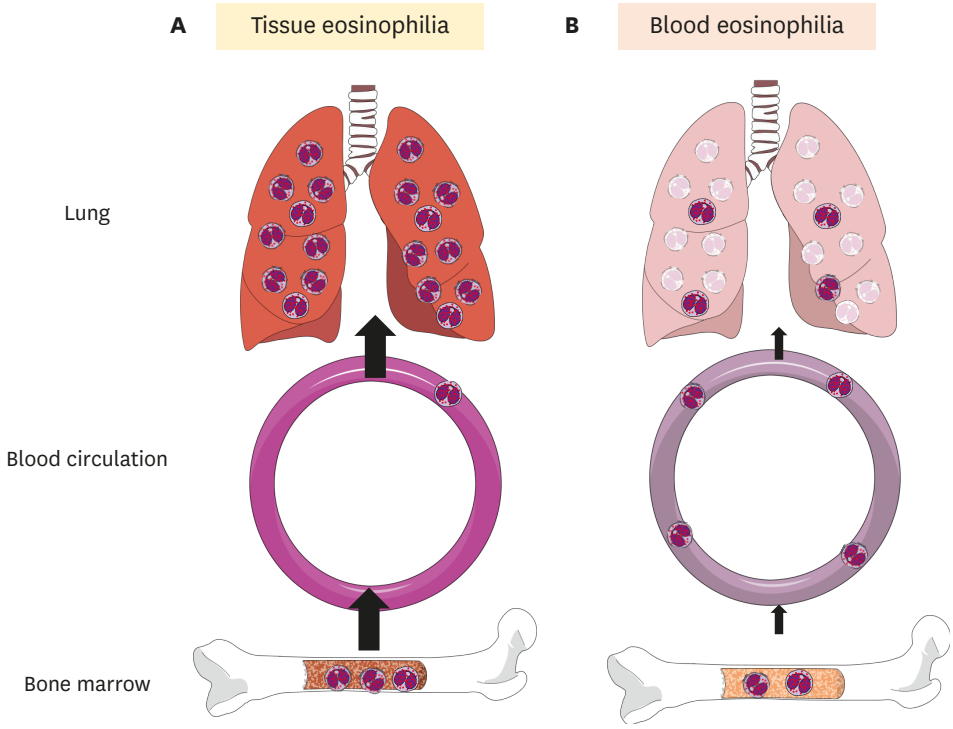

Fig. 2. Schematic of tissue and blood eosinophilia in acute eosinophilic pneumonia (AEP).
(**A**) At the onset of AEP, there is a rapid recruitment of blood eosinophils into the lung, resulting in a normal-range blood eosinophil count. (**B**) After treatment with systemic steroids, the eosinophilic lung inflammation is resolved, mainly through the induction of eosinophil apoptosis in the lungs. The decreased recruitment of blood eosinophils into the lung might result in the retention of eosinophils in circulation, leading to a transient blood eosinophilia.

serum IL-5 rapidly falls into the normal range within 10 days [126], whereas peripheral blood eosinophil counts increase with radiographic and clinical resolution during the following days [126, 133, 134].

Corticosteroids have various potent anti-inflammatory effects on allergic inflammation. They can induce eosinophil apoptosis directly as well as can indirectly, by inhibiting the production of survival factors including IL-5 [135, 136]. In addition, corticosteroids enhance the phagocytic capacity of macrophages and airway epithelial cells [136, 137]. Apoptotic eosinophils are intact when they are recognized and engulfed by phagocytes, so they do not induce inflammation [138]. As illustrated in **Fig. 2B**, after the treatment of AEP with a systemic steroid, eosinophilic lung inflammation is resolved, likely through the clearance of apoptotic eosinophils in the lungs. It is also conceivable that the decreased recruitment of blood eosinophils into the lungs results in a transient blood eosinophilia.

The mismatch of circulating and tissue eosinophilia is not limited to AEP. For instance, we have also experienced a case in which a patient with GM-CSF-producing lung cancer showed no clinical manifestations or evidence of tissue eosinophilia despite having marked blood eosinophilia (>30,000 cells/μL) [139]. Dupilumab, an anti-IL-4Rα antibody that blocks both IL-4 and IL-13 signaling, can trigger eosinophilia without the presentation of clinical signs of organ involvement owing to eosinophil infiltration [140]. The mechanisms underlying dupilumab-induced eosinophilia remain unknown, but it has been hypothesized that dupilumab blocks the migration of eosinophils into tissue without blocking eosinophil

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production in the bone marrow [141]. Hypereosinophilia is defined by a peripheral blood absolute eosinophil count of greater than 1,500 cells/μL that may not be associated with tissue damage [142]. In addition to patients with hypereosinophilic syndrome, who typically require treatment to prevent disease progression, there are patients with unexplained persistent asymptomatic hypereosinophilia. Additionally, clinical manifestation related to eosinophilic inflammation is uncommon in patients with familial eosinophilia [143]. Thus, the circulating eosinophil count does not always reflect tissue eosinophilia and vice versa.

"EOSINOPHILIC" TISSUE IN THE ABSENCE OF EOSINOPHILS

Tissue hypereosinophilia can be defined as tissue with a percentage of eosinophils that exceeds 20% of all nucleated cells in the bone marrow or tissue infiltration that is deemed extensive by a pathologist [11, 144]. However, historical studies with immunostaining for eosinophil granule proteins have revealed the extracellular deposition of granule proteins coincident with pathological conditions, even in the absence of a significant eosinophil infiltrate. Frigas ans Gleich [145] described the lung tissue specimens from autopsy cases who died of asthma as follows: "some eosinophils were intact, others were partially degranulated and surrounded by their extruded granules, and others were totally disrupted and unrecognizable by hematoxylin and eosin stain." In atopic patients challenged with an intradermal injection of allergen, MBP and EDN were extensively deposited throughout the dermis in the late-phase reaction [146]. Tissue deposition of granule protein in the absence of eosinophil accumulation has also been reported by Gleich et al. in cases of Hodgkin's disease [147], parasite infection [148, 149], chronic urticaria [150], atopic dermatitis [151], and endomyocardial disease [152]. Several studies have indicated that granule protein deposition, rather than intact eosinophils, is associated with tissue remodeling [153, 154]. Given the toxicity of eosinophil granule proteins, histologic evidence of extracellular granule protein deposition in the tissue might be a more appropriate marker for inflammation than tissue eosinophilia.

Our group has studied hundreds of tissues from patients with allergic or eosinophilic diseases [26, 29, 83, 84, 155-160]. In our tissue immunostaining experience, like Gleich et al., we have observed that the extracellular deposition of MBP is not disease-specific, but it is closely associated with tissue damage and the presence of eosinophil cytolysis. **Fig. 3** shows a typical example: surgically obtained nasal polyps from a case of chronic rhinosinusitis with nasal polyps (eosinophilic chronic rhinosinusitis). Hematoxylin and eosin staining revealed that the accumulated eosinophils were cytolytic, showing extracellular cell-free granules and chromatolysis and/or a loss of nuclear envelope. Immunostaining indicated a massive deposition of extracellular MBP that is consistent with the presence of cytolytic eosinophils. These cytolytic eosinophils were ultrastructurally identical to EETosis induced by various stimuli *in vitro* [26, 83].

Apoptosis facilitates the ingestion of intact eosinophils without a disgorgement of their toxic contents, and this process is necessary for the normal resolution of inflammation [138]. Impaired phagocytic clearance (efferocytosis) of lytic eosinophils is a critical feature of persistent inflammation. Notably, efferocytosis by phagocytic cells might not be applicable for ETotic cells, because of their rapid cell death process (0.5–3 hours) and lack of find-me signal exposure before cell lysis [25, 26]. Therefore, eosinophil cell fate within tissues might have completely different consequences (**Fig. 4**).

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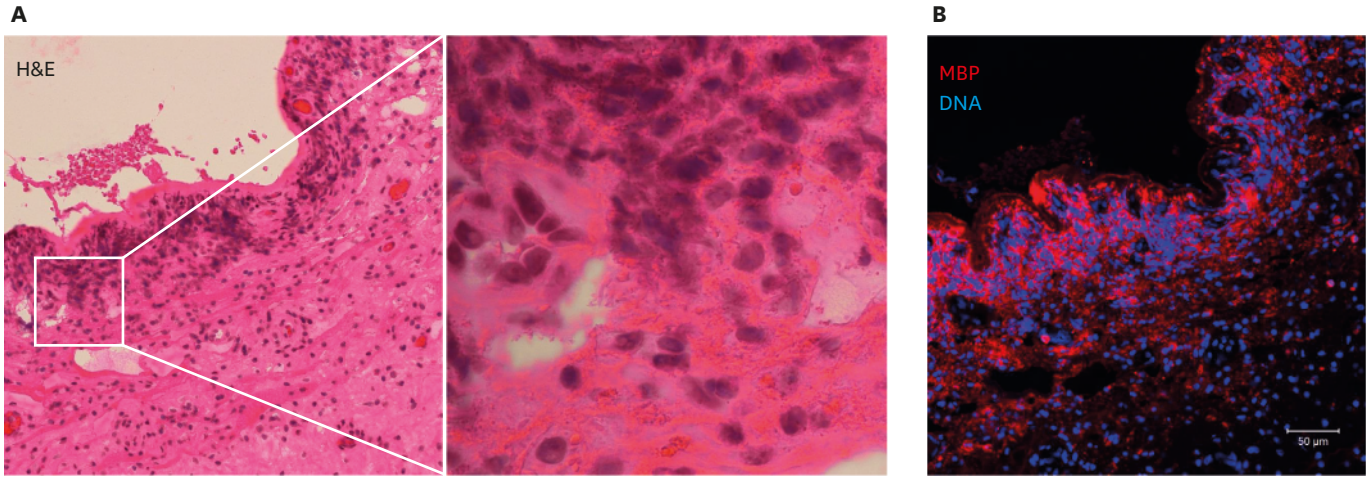

Fig. 3. Cytolytic eosinophils in a nasal polyp obtained from a case of chronic rhinosinusitis with nasal polyps (eosinophilic chronic rhinosinusitis).
(**A**) Hematoxylin and eosin (H&E) staining of a nasal polyp, showing a loss of epithelium and inflammatory cell infiltration in submucosal tissue. The boxed area in the left panel is shown magnified in the right panel. Accumulated cells showed cytolysis and a loss of nuclear shape (chromatolysis). Eosinophilic extracellular granules were also noted. (**B**) A serial section of the tissue shown in panel A was immunostained for major basic protein (MBP) (red) and counterstained for DNA (blue). Image was obtained with a Carl Zeiss LSM780 confocal microscope (×20). The massive deposition of extracellular MBP visible is consistent with the presence of cytolytic eosinophils.

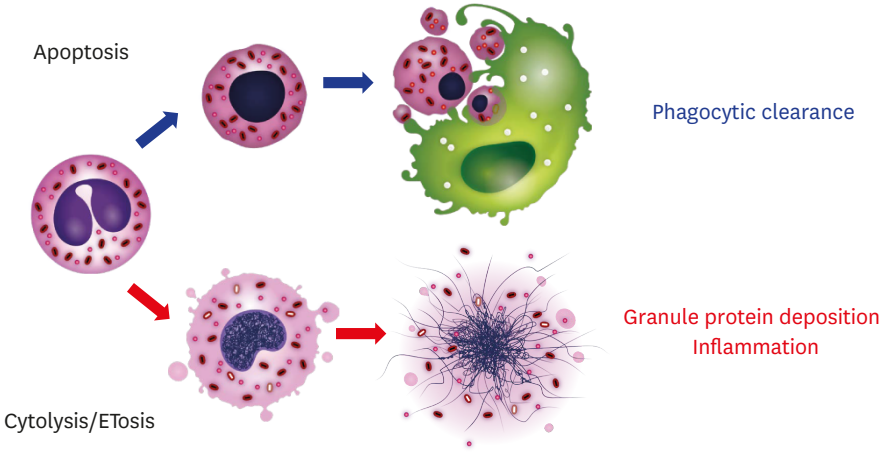

Fig. 4. Eosinophil cell fates and their consequences.
Eosinophils apoptosis can be caused by many factors, including aging, a loss of survival factors, corticosteroids, and anti-interleukin (IL)-5/anti-IL-5 receptor antibodies. Apoptotic eosinophils, typically with nuclear and cytoplasmic condensation, are phagocytosed without the induction of inflammation. Alternately, eosinophils can undergo ETosis upon activation, such as by an immunoglobulin-coated surface, pathogens, or platelet-activating factor with IL-5. Rapid cytolysis without the expression of a "find-me" signal results in the tissue deposition of the cell's total intracellular contents and prolonged inflammation.

CONCLUSIONS

The presence of eosinophils is an important feature of type-2 inflammation, but clinical observations have indicated that eosinophil-mediated inflammation is not always coincident with an increase in eosinophil counts. As shown in the case of AEP, there are various examples of mismatch between the circulating eosinophil count and clinical manifestation. As stated above, considerable evidence has indicated that the marked deposition of eosinophil granule proteins in tissue is associated with tissue damage and remodeling. The most important feature of eosinophils as end-stage effector cells is their activation to release

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toxic cellular contents. In this context, eosinophils can be innocent bystanders without the secretion of their bioactive mediators.

EETosis is now considered to be a major mechanism of cytolytic degranulation. This process is not only a total cell degranulation but also a release of cytoplasmic and nuclear contents, including DNA and histones that act as alarmins. Although the maintenance of tissue eosinophils is tightly related to the ability of the cell and the microenvironment to maintain an appropriate balance between survival and active cell death pathways, it is not yet fully understood. Further study will lead to a better understanding of eosinophil-mediated inflammation and its treatment.

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