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Mini Review

The roles of non-T-cells in infectious uveitis

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 Immune responses against uveitis are broadly divided into innate immune response and adaptive immune response. The group of inflammatory cells that induce innate immunity against uveitis comprises the "non-lymphocytes" such as neutrophils, macrophages and dendritic cells. Among the uveitis in which innate immunity plays a central role, infectious uveitis is the most important. Particularly in endophthalmitis and acute retinal necrosis that have poor visual prognosis, delay in diagnosis directly impacts visual function; therefore early diagnosis and treatment are important to obtain good visual outcome. Neutrophils are the inflammatory cells involved in the earliest pathology of infectious uveitis, causing ocular tissue damage which may result in irreversible visual function impairment. In representative infectious uveitis such as endogenous bacterial or fungal endophthalmitis, a characteristic cytokine profile has been identified; apart from cytokines promoting neutrophil migration, production and activation, other cytokines that enhance neuropathy and intraocular proliferation have also been detected. Although Behçet's disease has been considered to be a uveitis involving adaptive immunity, since the hypopyon observed in this disease is composed of neutrophils, inflammatory cells of the innate immune system are also involved in its pathology. However, considering also the fact that T cell infiltration features prominently in retinal vasculitis of Behçet's disease, innate immunity and adaptive immunity do not act individually, but function simultaneously and form an innate immunity-adaptive immune cycle, contributing to the persistence and chronicity of uveitis.

Introduction

Many inflammatory cells are involved in uveitis, and the etiologies of uveitis are also diverse spanning from autoimmune diseases to infections. The immune responses mediated by inflammatory cells are broadly divided into innate immunity and adaptive immunity[1]. In innate immunity, antigen — presenting cells such as macrophages and dendritic cells, neutrophils, and monocytes are activated by exposure to self-antigen, invasion by microorganisms or tissue damage, and produce cytokines including tumor necrosis factor

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(TNF) α and interleukin (IL)-6 as well as chemokines such as IL-8 and monocyte chemoattractant protein (MCP)-1. Following the early immune responses elicited by innate immunity, lymphocyte—dominant adaptive immunity is then induced which involves T cells and B cells. In other words, non-lymphocyte — dominant immune response is the immune response dominated by neutrophils, macrophages and dendritic cells, which mediate the innate immunity.

Among the diverse types of uveitis, this article focuses on the diseases that induce non-lymphocyte—dominant inflammatory responses, or diseases in which non-T-cells mechanisms are thought to play a central role.

Bacterial and fungal endophthalmitis

Neutrophil are well known as a representative of non-lymphocyte. Infectious uveitis is a type of uveitis in which neutrophils play a central role. Among infectious uveitis, bacterial and fungal endophthalmitis are the most important diseases that require differential diagnosis because delay in diagnosis and treatment may lead to blindness. However, since endophthalmitis is not a disease commonly encountered in routine clinical practice, accumulating sufficient experience of this disease presents some difficulties[2]. If a patient presents with infection within the eye which occurs after cataract surgery or vitrectomy, then the first suspicion would be postoperative endophthalmitis. However, approximately one-third of endogenous endophthalmitis cases do not arouse a suspicion until the inflammation becomes severe. Endophthalmitis is divided mainly into bacterial and fungal. The most common causative microorganisms are Gram negative bacteria such as *Klebsiella pneumoniae* and *Escherichia coli*, followed by fungi such as *Candida* species. While bacterial endophthalmitis caused mainly by *Klebsiella pneumoniae* and *Escherichia coli* shows rapid aggravation of inflammation, fungal endophthalmitis and bacterial endophthalmitis caused by low-virulence bacteria such as *Propionibacterium acnes* exhibit slow disease progression and the index of suspicion for endophthalmitis is generally low. Furthermore, by taking adrenal corticosteroids, inflammatory cells that have once infiltrated in response to fungal or low-virulence bacterial infection remit transiently. For this reason, it is not rare to see referred patients presenting with already deteriorated vision because they have been prescribed corticosteroids indiscriminately. In clinical practice, it has been reported that approximately one-half of endophthalmitis cases are misdiagnosed at initial presentations[2].
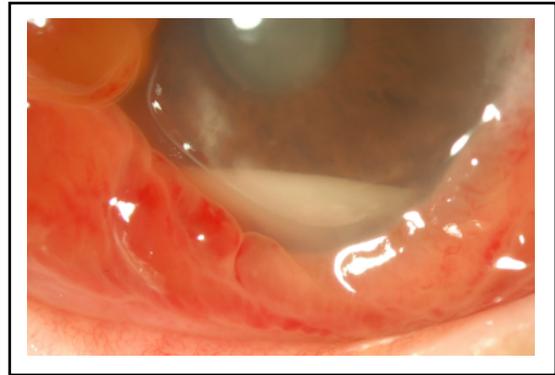

Fig.1   Metastatic endophthalmitis caused by beta hemolytic streptococci originated from bronchial abscess
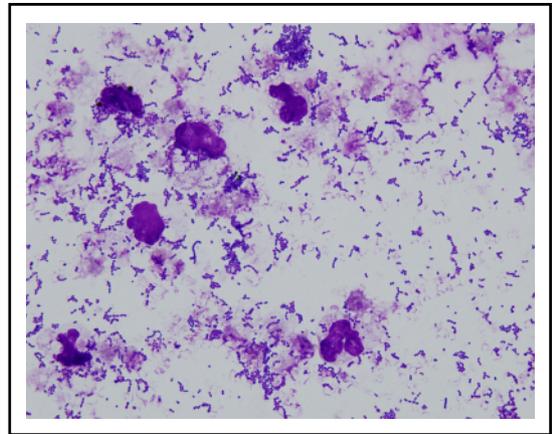Marked edema and hypopyon are observed

Fig.2   Marked infiltration by inflammatory cells, notably neutrophils, and many cocci forming chains are shown.

Moreover, in patients with slowly progressive endophthalmitis, a mixture of neutrophilic infiltration and lymphocytic infiltration may be observed. Therefore, rapidly progressive bacterial endophthalmitis and slowly progressive fungal and low-virulence bacterial endophthalmitis differ not only in clinical findings but also in the type of infiltrated inflammatory cells. Endogenous bacterial endophthalmitis that progresses rapidly occurs commonly in elderly patients with underlying diseases. Despite being granulomatous uveitis with mutton-fat keratic precipitates in unilateral eye, characteristic non-granulomatous uveitis findings of fibrin and hypopyon are also found (Fig. 1). Conjunctival chemosis is also a common finding.

In the initial disease stage, neutrophils and tissue mac-

rophages, dendritic cells and microglia initiate the earliest response against the bacteria or fungi that have invaded into the eye. Compared to other inflammatory cells, neutrophils characteristically migrate most rapidly (Fig. 2). On the other hand, tissue macrophages, dendritic cells and microglia in the retina become activated and secrete large quantities of cytokines and chemokines even before the inflammatory cells from the peripheral blood infiltrate the eye. As systemic inflammatory response, the number of neutrophils in the peripheral blood is often elevated compared to the normal range, whereas the number of lymphocytes is lower than the normal range. Other changes include increases in C-reactive protein (CRP) level and erythrocyte sedimentation rate (Table 1). Therefore, when an elderly person with some underlying diseases presents with the above-mentioned clinical picture together with elevated neutrophil count in peripheral blood and high serum CRP and erythrocyte sedimentation, then endophthalmitis should be suspected.

In the intraocular fluid of patients with bacterial or fungal endophthalmitis, the concentrations of cytokines such as MCP-1 and IL-8 that play important roles in the migration of neutrophils and macrophages are significantly elevated in the vitreous fluid. Moreover, the vitreous fluid concentration of granulocyte-colony stimulating factor (G-CSF) that stimulates the proliferation of granulocytes (represented by neutrophils) and enhances functions of neutrophils is significantly higher compared to patients with other uveitis. Therefore, G-CSF in ocular fluids may be a useful diagnostic marker for endogenous endophthalmitis. In additional to the above cytokines, the concentrations of basic fibroblast growth factor (bFGF) that is known to be growth factors, and interferon (IFN)γ and TNFα that not only activates T cells but also mediates neuropathy are also elevated in the vitreous fluid (Table 2). The resultant strong proliferative changes in the intraocular environment contribute to the poor visual outcome.

Toll-like receptor (TLR) is a mechanism by which neutrophils and macrophages / dendritic cells / microglia recognize microorganisms. When stimulated, TLR activates neutrophils and macrophages / dendritic cells / microglia, potently inducing cytokine production. By producing cytokines, neutrophils and macrophages / dendritic cells / microglia indiscriminately damage tissues including normal tissues that are not affected by infection. Especially, neutrophils produce tissue damaging factors including myeloperoxidase (MPO) and elastase. Once these enzymes are released, they produce severe irreversible damages to ocular tissues. In addi-

Table 1 Elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in endophthalmitis

Apart from ophthalmoscopic findings are not significant different between endophthalmitis and acute anterior uveitis, but CRP and ESR are higher in endophthalmitis.

Bacterial endophthalmitis		Acute anterior uveitis
CRP 7.6±6.1	$p<0.0001$	CRP 1.7±1.5
ESR 75±28		ESR 24±18
	$p<0.0001$	

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate

tion, even after neutrophils undergo apoptosis, the tissue damaging effect continues. The more inflammatory cells infiltrate intraocular tissues, the more cells will die from treatment, with a possibility that the leaked intranuclear DNA-binding protein augments TLR stimulation of self-DNA. Marked retina necrosis is observed in endophthalmitis, and this necrosis is also not solely due to direct retinal damage by the bacteria. In other words, in endophthalmitis, in additional to tissue damage caused by the pathogens, the neutrophils that are intended to remove the bacteria also participate in tissue damage, aggravating the ocular lesions. Early treatment is absolutely essential.

Parasitic (toxoplasma and toxocara) uveitis

Representative parasitic uveitis include ocular toxocariasis caused by *Toxocara canis* or *Toxocara catis*, and ocular toxoplasmosis caused by *Toxoplasma gondii*. Although the intraocular tissues are infiltrated by diverse inflammatory cells such as lymphocytes, macrophages and plasma cells, intraocular infiltration by eosinophils is a feature distinct from other types of uveitis. However, increased eosinophil count in peripheral blood and elevated IgG, which are commonly observed in general parasitic infections, are not necessary present in all cases of parasitic uveitis, with many showing normal findings. When eosinophils are detected in intraocular fluid of uveitic eye, the possibility of parasitic uveitis should be investigated. Especially when vitreous opacity is strong, a yellowish white mass of eosinophilic abscess may be ob-

Table 2 Immune mediator levels in vitreous samples of patients with endogenous endophthalmitis and uveitis

	endogenous endophthalmitis (n = 19)	uveitis (n = 26)	p values
Angiogenin (pg/ml)	11953.3 (2342.0-17810.2)	7639.1 (3866.8-9422.7)	0.8903
bFGF (pg/ml)	220.6 (0-219.5)	5.5 (0-11.4)	0.0345
G-CSF (pg/ml)	1995.8 (146.7-4576.8)	9.8 (0-4.7)	<0.0001
GM-CSF (pg/ml)	0 (0-0)	0 (0-0)	1.000
Granzyme A (pg/ml)	91.0 (0-60.7)	486.3 (1.6-42.7)	0.8813
Granzyme B (pg/ml)	88.9 (0-88.7)	66.4 (0-52.0)	0.7827
IFN γ (pg/ml)	62.3 (1.0-78.2)	15.1 (0-18.0)	0.0444
IL-6 (pg/ml)	23221.2 (1937.4-32337.6)	825.1 (128.6-912.7)	0.0001
IL-8 (pg/ml)	13068.8 (656.1-8373.5)	372.0 (58.1-352.9)	<0.0001
IL-10 (pg/ml)	53.6 (0-55.3)	21.7 (6.0-24.6)	0.5274
IP-10 (pg/ml)	27167.4 (1708.3-100124.0)	42859.8 (1708.3-100124.0)	0.4414
MCP-1 (pg/ml)	8874.6 (1596.5-10992.0)	1878.4 (848.4-2908.6)	0.0037
TNF α (pg/ml)	106.1 (0-13.3)	0.1(0-0)	0.0075
VEGF (pg/ml)	4410.4 (0.2-818.9)	140.9 (0-66.3)	0.2104

Immune mediator levels are expressed as mean with interquatile range in parenthesis.
bFGF = basic fibroblast growth factor; G-CSF = granulocyto-colony stimulating factor;
GM-CSF = granulocyte macrophage-colony stimulating factor; IFN = interferon;
IL = interleukin; IP-10 = interferon gamma-induced protein 10 kDa;
MCP = monocyto chemoattractant protein; TNF = tumor necrosis factor;
VEGF = vascular endothelial growth factor

served. Although eosinophil infiltration is speculated to be a response to the parasite, toxoplasma-specific T lymphocytes also contribute to the pathology of this disease.

When parasitic uveitis is suspected, careful history taking is important, such as asking whether the patient "has been in the sand pit of the park", "has had contact with pets", or "has eaten raw meat".

Acute retinal necrosis

Acute retinal necrosis (ARN) syndrome is a rare disease that was diagnosed in only 1.3% of 3060 endogenous uveitis patients attending university hospitals in Japan during the year 2002[4]. ARN is a disease with very poor visual prognosis[5]. As for the pathogenesis of ARN, it was unclear why herpes virus that has infected and remained inactive in most adults causes ARN in healthy people with normal immunocompetence. However, Kittan et al[6]. reported that ARN patients showed reduced production of type I IFN that is important in defense against herpes virus, and reduction in number of plasmatoid dendritic cells that express TLR7 and TLR9; consequently the host is unable to prevent reactivation of the latently infected herpes virus, resulting in onset of ARN.

Especially, dendritic cells have greater antigen-presenting capability than macrophages and augment immune response; hence they play a very important role in the immune response against infection during the early disease stage. In normal mice, since dendritic cells distribute widely in the cornea, uvea, retina, and other intraocular tissues, they may be also associated closely with the induction and aggravation of uveitis other than ARN. Further elucidation of this hypothesis is anticipated.

Conclusion

In lymphocyte — dominant uveitis represented by sarcoidosis and Vogt-Koyanagi-Harada, and intraocular lymphoma represented by masquerade syndrome, increased concentrations of cytokines such as IL-8 and MCP-1 have been observed, and these cytokines play important roles in the migration of neutrophils and macrophages that induce innate immunity[7-9]. Therefore in an environment where adaptive immunity is induced, neutrophils and macrophages (which suggest simultaneous induction of innate immunity) not only participate in infection immunity but also serve as a bridge to adaptive immunity mediated by lymphocytes. Fur-

ther research on non-lymphocyte inflammatory response is expected to lead to the elucidation of pathologic mechanisms and development of novel therapeutic strategies for endophthalmitis that is visually threatening and also for lymphocyte—dominant uveitis. However, no matter how medicine is going to advance, the importance of early diagnosis by an ophthalmologist will remain unchanged in the future.

Disclosure of potential conflicts of interest

None

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