

[ CASE REPORT ]

## Cytokine Profile in Sweet's Syndrome under the Treatment of Pulmonary Toxoplasmosis Complicated with Myelodysplastic Syndrome

Yukimasa Matsuzawa<sup>1</sup>, Eisuke Adachi<sup>1</sup>, Atsuko Takahashi<sup>2</sup>, Hidenori Sato<sup>1</sup>, Lay Ahyoung Lim<sup>1</sup>, Tsunehiko Komatsu<sup>3</sup>, Tomohiko Koibuchi<sup>1</sup>, Tokiko Nagamura-Inoue<sup>2</sup>, Arinobu Tojo<sup>4</sup>, Hitomi Nagayama<sup>5</sup> and Hiroshi Yotsuyanagi<sup>1</sup>

### Abstract:

We herein describe a case of Sweet's syndrome (SS) in a patient being treated for pulmonary toxoplasmosis complicated with myelodysplastic syndrome (MDS). The patient's SS developed after the pulmonary toxoplasmosis improved following treatment. We searched his cytokine profiles comprehensively using a bead-based immunoassay. The results showed no elevation of interleukin (IL)-2, interferon (IFN)- $\gamma$  or IL-17 A, and IL-6 was only observed to have increased at the onset of SS, suggesting that the pulmonary toxoplasmosis had been well controlled and that chronic inflammation may have been the cause of SS. Pulmonary toxoplasmosis is an extremely rare occurrence. The cytokine profile can help to clarify the pathological condition of SS and MDS complicated with severely invasive infectious diseases.

**Key words:** Sweet's syndrome, toxoplasmosis, cytometric bead array, myelodysplastic syndrome

(Intern Med 58: 2079-2083, 2019)

(DOI: 10.2169/internalmedicine.2372-18)

### Introduction

Sweet's syndrome (SS) is a rare condition and a distinct disorder which is defined by four clinical features: fever, neutrophilic leukocytosis, the sudden onset of painful erythematous skin lesions, and dense dermal infiltrate of neutrophils (1). The exact cause of SS is still unknown, but some patients have underlying chronic inflammatory diseases and SS is thus thought to be triggered by acute infectious diseases and certain medications (2, 3). SS may arise in association with a variety of underlying systemic diseases and it sometimes occurs as a paraneoplastic syndrome in other hematological conditions such as myelodysplastic syndrome (MDS) (2). In addition, a nonspecific upper respiratory tract infection frequently precedes the appearance of a

rash, and specific comorbid infections have also occasionally been identified (4, 5).

Toxoplasmosis is a parasitic disease caused by *Toxoplasma gondii* (*T. gondii*). Among severely immunocompromised patients, disseminated toxoplasmosis can occur following a primary infection or the reactivation of latent tissue cysts (6). Pulmonary involvement is extremely rare, and there are no reports of SS associated with pulmonary toxoplasmosis and MDS. One report showed that febrile neutrophilic dermatosis associated with toxoplasmosis successfully resolved after the treatment of pyrimethamine and sulfadiazine (7). SS could be caused by uncontrolled pulmonary toxoplasmosis through a robust type 1 helper (Th1) immune reaction (8). In addition, some reports showed that rare infectious diseases, such as a pulmonary fungal infection, could trigger the development of SS (4).

<sup>1</sup>Department of Infectious Diseases and Applied Immunology, IMSUT Hospital of The Institute of Medical Science, The University of Tokyo, Japan, <sup>2</sup>Department of Cell Processing and Transfusion, The Institute of Medical Science, The University of Tokyo, Japan, <sup>3</sup>Department of Hematology, Joban Hospital of Tokiwakai Group, Japan, <sup>4</sup>Department of Hematology/Oncology, Research Hospital The Institute of Medical Science, The University of Tokyo, Japan and <sup>5</sup>Department of Hematology, Teikyo University Chiba Medical Center, Japan

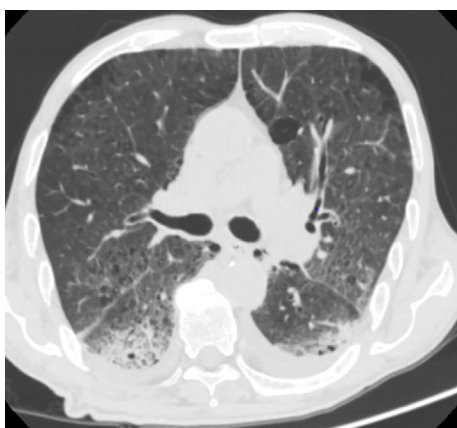
Received: November 12, 2018; Accepted: January 21, 2019; Advance Publication by J-STAGE: March 28, 2019

Correspondence to Dr. Eisuke Adachi, eadachi-ims@umin.ac.jp

We herein report a case of SS in a patient that was being treated for suspected pulmonary toxoplasmosis complicated with MDS. The cytokine profile is essential to clarify the pathological condition of SS and MDS complicated with severe invasive infections. A bead-based immunoassay enabled us to quantitatively detect multiple analytes using a single serum (9). It is a powerful tool for detecting multiple cytokines comprehensively. In this report, we searched interleukin (IL)-2, IL-4, IL-6, IL-10, IL-17A, tumor necrosis factor (TNF), and interferon (IFN)- $\gamma$ , in order to select the optimal treatment course and to elucidate the immunological relationship between anti-*Toxoplasma* immune reaction and SS associated with MDS.

### Case Report

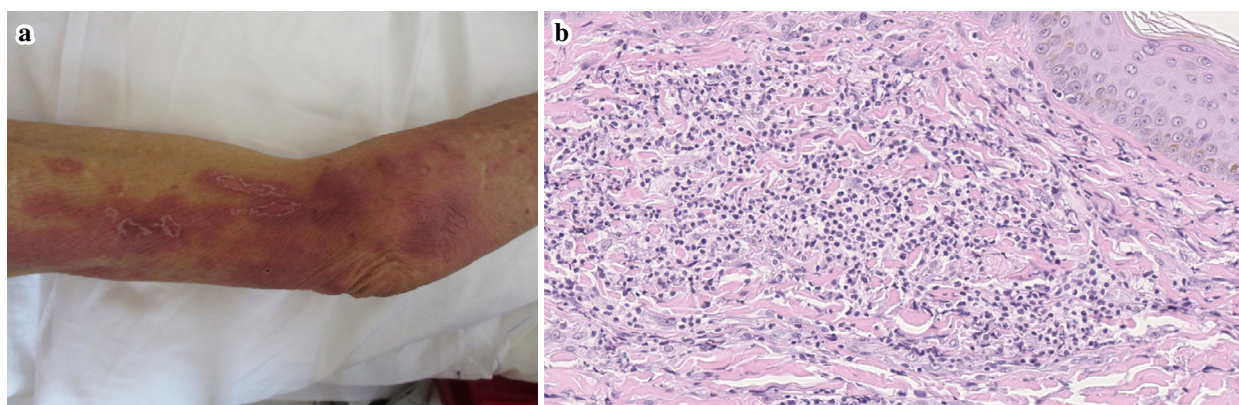
A 74-year-old male patient was referred to the hematology department of a general hospital for an assessment of fever and anemia. A bone marrow examination showed markedly increased dysplastic erythroblasts, increased mitosis and megaloblastic change with nuclear-cytoplasmic asyn-



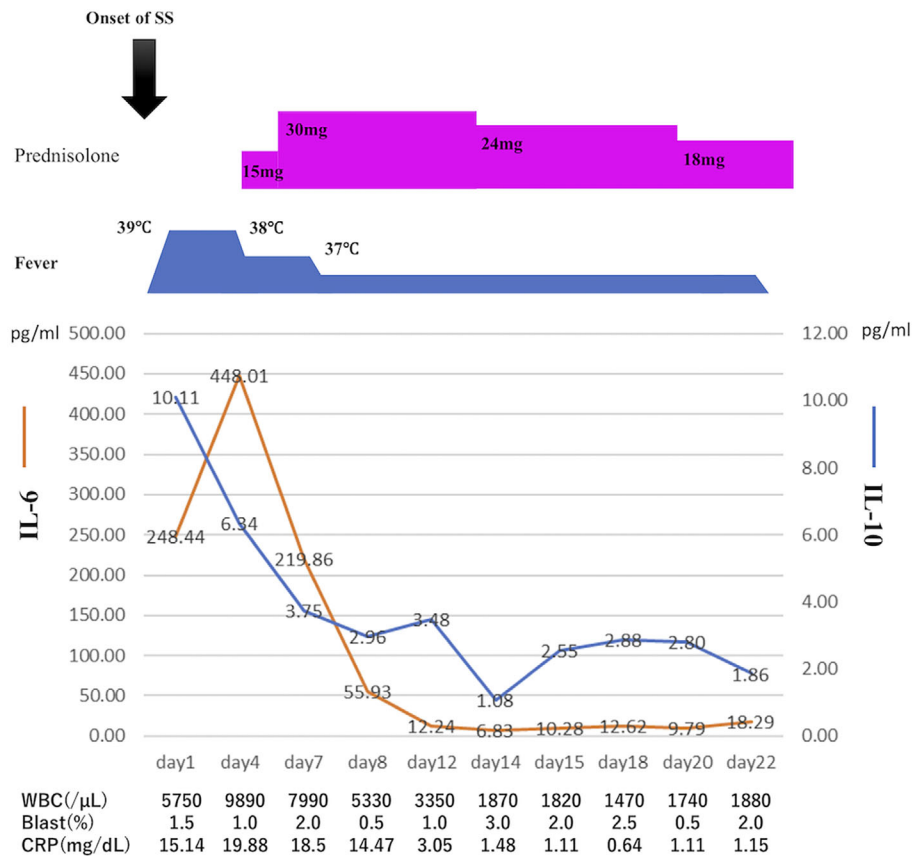
**Figure 1.** Chest computed tomographic findings before the treatment of toxoplasmosis show bilateral ground-grass opacities and pleural effusion.

chronicity, suggesting MDS. A karyotype analysis indicated complex chromosomal abnormalities of 46, XY, -3, -5, add (7)(p22), -12, del(16)(q22), add(17)(q25), -19, +mar[11] 11 cells out of 20 cells, and he was diagnosed to have refractory cytopenia with multilineage dysplasia (RCMD) as defined by the WHO 5th MDS criteria. On admission, he complained of fever with difficulty in breathing. Computed tomography (CT) indicated patchy ground-glass opacities with septal thickening and a lower lobe distribution in both lungs, as shown in Fig. 1. Piperacillin/tazobactam as the empirical antibiotic therapy was administered, though the fever persisted without any improvement in the radiological findings. Serological tests for *Candida*, *Aspergillus*, and  $\beta$ -D-glucan were all negative. Nonetheless, the patient reported that he often fed stray cats as pets and thus had been in daily contact with unvaccinated street cats, anti-*Toxoplasma* immunoglobulin-M (IgM) and immunoglobulin-G (IgG) was positive according to an enzyme immunoassay (EIA). He was therefore referred to our hospital for the further evaluation and to receive treatment for lung toxoplasmosis. After being transferred, we administered pyrimethamine 50 mg/day and sulfadiazine 4 g/day as an induction therapy for lung toxoplasmosis. Accordingly, his fever subsided, and the CT findings showed an improvement of pneumonia. Sputum cultures and blood bacterial and fungal cultures were all negative. His anti-*Toxoplasma* IgG elevated from 69 IU/mL to 201 IU/mL 26 days after the initial examination, and therefore acute lung toxoplasmosis was suspected.

Several dark-red eruptions appeared on his bilateral upper arms 23 days after the initiation of the treatment for toxoplasmosis (Fig. 2a). We suspected a drug allergy to sulfadiazine at first and thus changed his medication to atovaquone 3,000 mg/day. However, the rashes thereafter expanded, and we therefore performed a skin biopsy from the wheals, and it revealed the infiltration of neutrophils in the subcutaneous fat without vasculitis (Fig. 2b). Our patient fulfilled the criteria of SS as proposed by Su and Liu (10). He demonstrated two major criteria: (i) An abrupt appearance of papules and/or painful erythematous plaques; and



**Figure 2.** Skin lesions of Sweet's syndrome. a: Dark-red eruptions appeared on his bilateral upper arms at the onset of Sweet's syndrome. b: The microscopic findings of a skin biopsy show the infiltration of neutrophils in the subcutaneous fat without vasculitis. Magnification,  $\times 400$ .



**Figure 3.** Cytokine profiles and the clinical course. SS: Sweet's syndrome, WBC: white blood cell, IL: interleukin, CRP: C-reactive protein

(ii) Histological evidence of dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis. As a result, we started prednisolone of 30 mg/day. The rashes immediately disappeared. Meanwhile, his general condition including loss of appetite improved, and thus we decreased the amount of prednisolone to 18 mg/day. His clinical findings were compatible with four minor criteria: (i) General malaise and fever ( $>38^{\circ}\text{C}$ ); (ii) An association with hematologic malignancy (MDS); (iii) An excellent response to systemic corticosteroids; and (iv) Abnormal laboratory values (positive C-reactive protein,  $>8,000/\mu\text{L}$  of leukocytes, segmented-nuclear neutrophils and stabs  $>70\%$  in peripheral blood smear. After the onset of SS, we measured the cytokine profiles by using a bead-based immunoassay (Human Th1/Th2/Th17 Cytokine Kit, BD™ Cytometric Bead Array, BD Biosciences Pharmingen, San Diego, United States). Fig. 3 showed that IL-6 had increased at the onset of SS. After the initiation of prednisolone, IL-6 decreased promptly, yet it remained at a low level and did not become undetectable in spite of the subsequent improvement of fever and rashes. IL-10 had been detected simultaneously. The levels of IL-2, IL-4, IL-17A, TNF and IFN- $\gamma$  were all under the detection limit (data not shown). There was no exacerbation of lung toxoplasmosis, and after six weeks of induction therapy, we started atovaquone 1,500 mg/day as maintenance therapy. An acute myelocytic leukemic transformation occurred 50 days after the initiation of the treatment for toxoplasmosis.

## Discussion

The etiology of SS is still unclear. It is well known that an excessive activation of neutrophils and an abnormal distribution of endogenous cytokine is observed in SS patients (11). The twenty percent of SS cases have malignant diseases such as MDS, myelofibrosis and acute myeloid leukemia (AML) (2). In MDS case, refractory anemia with excessive blasts (RAEB) and RAEB in transformation (RAEB-t) are likely to be associated with the onset of SS. Among RAEB-t patients, the IL-6 concentrations are significantly higher than those seen in RA patients, and this seems to be a sign of a poor prognosis (12).

In this case, the diagnosis of toxoplasmosis was based on four reasons. First, the patient had a history of feeding unvaccinated stray cats. The contact with the oocysts in the feces of infected cats is a risk factor of *T. gondii* infection. Secondly, there was a therapeutic effect in the treatment with specific drugs for toxoplasmosis, while his pneumonia did not respond to the antibiotic therapy. Thirdly, anti-*Toxoplasma* IgM was positive, and IgG had been elevated during his clinical course. Finally, The 18S ribosomal DNA fragment of *T. gondii* was detected in the sputum sample, by a polymerase reaction (PCR) assay (13). However, we failed to confirm the sequence of the PCR product, because a sufficient volume of sample was not obtained. *T. gondii* infec-

tion in immunocompromised hosts often becomes lethal. Lung involvement is extremely rare, but it is known to be complicated in severely immunocompromised patients, such as hematopoietic stem cell transplantation (HSCT) recipients (14). Toxoplasmosis is an opportunistic infection that induces a strong cellular immune response. Cell-mediated immunity is essential for host resistance against *T. gondii*. A European report showed the prevalence of pulmonary toxoplasmosis among HIV-infected patients of 0.5-0.6% (6). In host immunity, the structural component of *T. gondii* is recognized by Toll-like receptor (TLR) 11, and innate immunity cells induce a large number of IL-12 as proinflammatory cytokines, and they also activate Th1 immune reaction, thus producing INF- $\gamma$ , IL-2 and related proteins (15). The cytokine pattern and IL-17-expressing CD4<sup>+</sup> and CD8<sup>+</sup> T cells may play an important role in the inflammatory response to human toxoplasmosis (16), while regulatory T cells and IL-17A play a key role in the pathology of ocular toxoplasmosis (17).

SS is an idiopathic, disease-associated, drug-induced, or infectious disease related disorder. Some specific underlying infections could trigger SS (3). A condition of comorbid infectious disease is important for treating SS because immunosuppressive therapy with corticosteroids is usually needed. In this case, we searched for cytokines comprehensively to elucidate the development course of these rare complications. Toxoplasmosis induces a robust Th1 immune reaction (8), but the result of this patient's cytokine array showed no elevation of IL-2 or IFN- $\gamma$  at the onset of SS, which thus suggested that anti-*Toxoplasma* immune reaction was suppressed during the clinical course of SS. His pulmonary toxoplasmosis was well controlled at the onset of SS. In contrast, the only IL-6 was observed to have increased along with the symptoms of SS and the elevated IL-6 levels decreased after the initiation of prednisolone (Fig. 3). The clinical course of our case was consistent with previous reports describing that only the IL-6 levels were elevated prior to prednisolone therapy and then the elevated interleukin-6 levels gradually decreased following therapy (18-20). Additionally, in this case, the IL-6 was already high at the onset of SS and not normalized after obtaining an improvement of the symptoms, thus suggesting the existence of chronic inflammation. On the basis of these findings, we infer that the development of SS in our patient was related to the rise of IL-6. Hattori et al. reported that the high level of G-CSF could explain leukocytosis, neutrophilic dermatosis, and IL-6 induced the associated symptoms of recurrent fever and pain in an SS patient (21). The blast crisis of MDS could be related to the development of SS, and we infer that blast crisis may thus have caused the SS in this case.

On the other hand, drug-induced SS was unlikely from the aspect of his cytokine profile, because his IL-2, IFN- $\gamma$ , and IL-17A showed no elevation at the onset of SS. IL-2, IFN- $\gamma$ , IL-17A activates macrophages and cytotoxic T cells and induces type IV allergies (22). It is equally unlikely that drug allergy caused SS on the basis of this cytokine profile.

Therefore, a comprehensive analysis of cytokines may help to exclude the drug eruption in the diagnosis of SS.

The role of the detectable low-level IL-10 was unclear (23). IL-10 has been shown to be a dominant immunoregulatory mechanism preventing Th1 immune reaction (24). Reports regarding IL-10 in SS are limited. In contrast, there are some reports describing the role of IL-10 in Th1 immune reaction to toxoplasmosis. Gaddi et al. proposed that when encountering *T. gondii*-infected cells, Th1 cells first produce IFN- $\gamma$  which then induces antigen-presenting cell's costimulatory activity for reactivating IL-10 gene expression in the same Th1 cell population (25). In this case, the levels of IL-10 were detectable but very low, and this finding might explain the healing process of inflammation and an anti-inflammatory reaction to the excessive activation of neutrophils.

IL-6 plays a crucial role in the acute phase response and the transition from acute to chronic inflammation. The dysregulation of IL-6 production is a major contributor to the pathogenesis of the chronic inflammatory condition associated with immunodeficiency diseases. Some reports have shown that IL-6 was also a biomarker for the mortality of HIV patients, and the chronic complications in patients with HIV were related to the overproduction of IL-6 (26, 27).

We herein described a case of SS complicated with MDS and pulmonary toxoplasmosis. The cytokine array can describe how the human immune system works against inflammation or the invasion of pathogens. Considering complicated situations similar to our case, a comprehensive analysis of cytokines helps to elucidate the pathogenesis and thus makes it possible to select the optimal treatment to successfully manage such cases.

**The authors state that they have no Conflict of Interest (COI).**

#### Acknowledgement

We would like to thank the tropical research and treatment group which provided us with the pyrimethamine and sulfadiazine for the treatment of toxoplasmosis.

#### References

1. Sweet RD. An acute febrile neutrophilic dermatosis. *Br J Dermatol* **76**: 349-356, 1964.
2. Kawakami T, Kawase A, Takeuchi S, et al. Sweet syndrome subsequent to relapsing polychondritis and myelodysplastic syndrome in a Japanese patient. *Acta Derm Venereol* **88**: 517-519, 2008.
3. Cohen PR. Sweet's syndrome—a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis* **2**: 34, 2007.
4. DiCaudo DJ, Ortiz KJ, Mengden SJ, Lim KK. Sweet syndrome (acute febrile neutrophilic dermatosis) associated with pulmonary coccidioidomycosis. *Arch Dermatol* **141**: 881-884, 2005.
5. Nelson CA, Noe MH, McMahon CM, et al. Sweet syndrome in patients with and without malignancy: a retrospective analysis of 83 patients from a tertiary academic referral center. *J Am Acad Dermatol* **78**: 303-309.e304, 2018.
6. Rabaud C, May T, Lucet JC, Lepout C, Ambroise-Thomas P, Canton P. Pulmonary toxoplasmosis in patients infected with human immunodeficiency virus: a French National Survey. *Clin In-*

- fect Dis **23**: 1249-1254, 1996.
7. Delfino M, Suppa F, De Luca F, Lembo G. Sweet's syndrome and toxoplasmosis: a coincidental association? *Dermatologica* **171**: 102-105, 1985.
  8. Dupont CD, Christian DA, Hunter CA. Immune response and immunopathology during toxoplasmosis. *Semin Immunopathol* **34**: 793-813, 2012.
  9. Morgan E, Varro R, Sepulveda H, et al. Cytometric bead array: a multiplexed assay platform with applications in various areas of biology. *Clin Immunol* **110**: 252-266, 2004.
  10. Su WP, Liu HN. Diagnostic criteria for Sweet's syndrome. *Cutis* **37**: 167-174, 1986.
  11. Marzano AV, Fanoni D, Antiga E, et al. Expression of cytokines, chemokines and other effector molecules in two prototypic autoimmune inflammatory skin diseases, pyoderma gangrenosum and Sweet's syndrome. *Clin Exp Immunol* **178**: 48-56, 2014.
  12. Herold M, Schmalzl F, Zwierzina H. Increased serum interleukin 6 levels in patients with myelodysplastic syndromes. *Leuk Res* **16**: 585-588, 1992.
  13. Filisetti D, Gorcii M, Pernot-Marino E, Villard O, Candolfi E. Diagnosis of congenital toxoplasmosis: comparison of targets for detection of *Toxoplasma gondii* by PCR. *J Clin Microbiol* **41**: 4826-4828, 2003.
  14. Sumi M, Norose K, Hikosaka K, et al. Clinical characteristics and computed tomography findings of pulmonary toxoplasmosis after hematopoietic stem cell transplantation. *Int J Hematol* **104**: 729-740, 2016.
  15. Yarovinsky F, Kanzler H, Hieny S, Coffman RL, Sher A. Toll-like receptor recognition regulates immunodominance in an antimicrobial CD4<sup>+</sup> T cell response. *Immunity* **25**: 655-664, 2006.
  16. Silva JL, Rezende-Oliveira K, da Silva MV, et al. IL-17-expressing CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes in human toxoplasmosis. *Mediators Inflamm* **2014**: 573825, 2014.
  17. Sauer A, Pfaff AW, Villard O, et al. Interleukin 17A as an effective target for anti-inflammatory and antiparasitic treatment of toxoplasmic uveitis. *J Infect Dis* **206**: 1319-1329, 2012.
  18. Reuss-Borst MA, Pawelec G, Saal JG, Horny HP, Muller CA, Waller HD. Sweet's syndrome associated with myelodysplasia: possible role of cytokines in the pathogenesis of the disease. *Br J Haematol* **84**: 356-358, 1993.
  19. Loraas A, Waage A, Lamvik J. Cytokine response pattern in Sweet's syndrome associated with myelodysplasia. *Br J Haematol* **87**: 669, 1994.
  20. Takano Y, Fujino H, Yachie A, Sumimoto SI. Serum cytokine profile in pediatric Sweet's syndrome: a case report. *J Med Case Rep* **11**: 178, 2017.
  21. Hattori H, Hoshida S, Yoneda S. Sweet's syndrome associated with recurrent fever in a patient with trisomy 8 myelodysplastic syndrome. *Int J Hematol* **77**: 383-386, 2003.
  22. Akhmaltdinova LL, Gazalieva MA, Akhmetova SB. Levels of cytokines in drug hypersensitivity. *Cent Eur J Immunol* **42**: 354-357, 2017.
  23. Kleiner G, Marcuzzi A, Zanin V, Monasta L, Zauli G. Cytokine levels in the serum of healthy subjects. *Mediators Inflamm* **2013**: 434010, 2013.
  24. Trinchieri G. Interleukin-10 production by effector T cells: Th1 cells show self control. *J Exp Med* **204**: 239-243, 2007.
  25. Gaddi PJ, Yap GS. Cytokine regulation of immunopathology in toxoplasmosis. *Immunol Cell Biol* **85**: 155-159, 2007.
  26. Borges AH, Silverberg MJ, Wentworth D, et al. Predicting risk of cancer during HIV infection: the role of inflammatory and coagulation biomarkers. *Aids* **27**: 1433-1441, 2013.
  27. Kuller LH, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med* **5**: e203, 2008.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).