Author's response to reviews

Title: Successful treatment in a case of Propionibacterium acnes-associated sarcoidosis with clarithromycin (CAM) administration: a case report

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Author's response to reviews:

This paper describes a case of sarcoidosis, in which a drastic improvement was achieved by clarithromycin (CAM) administration. It includes very important information from clinical and pathological points of view. The authors emphasize the following points described below.

1) This is the first case report of sarcoidosis in which a drastic improvement was achieved by a single clarithromycin (CAM) administration. There is no report documenting its drastic effectiveness for sarcoidosis in the literature.

2) CAM is known to have immunomodulatory and immunosuppressive effects. Recently, it has been applied to the treatment of neoplastic diseases such as multiple myeloma and advanced lung cancer. Especially, CAM has been widely incorporated into the BiRD therapy for treating multiple myeloma and a higher complete remission response rate has been obtained. In 2012, we first reported a case of Hodgkin-like lymphoma in which complete remission was achieved by CAM administration, and have emphasized its immunomodulatory and immunosuppressive effects. Thus far, many clinicians empirically have used CAM for the treatment of such neoplastic diseases without knowing the precise mechanism of its action. They are really willing to know its exact mechanism. In this study, we demonstrated that CAM has an apoptosis-inducing effect by detailed pathological analysis of a biopsied lymph node. This case report is the first document demonstrating an apoptotic effect of CAM clinically. In addition, we briefly reviewed the mechanism of CAM action.

3) In this case, the diagnosis of sarcoidosis was made based on the presence of non-caseating epitheloid cell granulomas with abundant Langhans giant cells in the lymph node. In addition, we demonstrated the presence of P. acnes in sarcoid granulomas in the lymph node. This finding indicates that sarcoid reaction was caused by P. acnes infection. Although histopathologic evidence is mandatory for a definitive diagnosis of sarcoidosis, non-caseating granulomas are also known to be found in a number of infectious diseases. We excluded the possibility of various infectious diseases by serological and histologic tests for
these diseases. Thus, this case does not represent a simple infectious disease but represents the hyperimmune disease by P. acnes infection.

4) In the process of pathological analysis of the biopsied lymph node, authors found that immunoglobulins were incorporated in Langhans giant cells. The incorporation may reflect the degree of degeneration of the giant cells. This finding is also the first document, though the exact mechanism and its significance remain uncertain.

5) Finally, we emphasize that this is an original case report, and it will have a broad impact across more than one area of medicine from clinical, pathological, pharmacological and immunological points of view.

To the Editor-in-Chief

We would like to thank the reviewer, especially Dr. G. Papaetis for thorough reading the manuscript and helpful suggestions in many points. We revised the manuscript according to his suggestions. Consequently, considerable portions were changed and new descriptions were added. Changed words and sentences are highlighted in blue and newly inserted words and sentences are written in red. The date was appropriately changed or removed in the Case Presentation section and Figure files to protect the anonymity of the patient. In addition, the manuscript was checked again by a native speaker.

The answers to the questions of Dr. G. Papaetis are described below.

1) Chest CT and XP images were added in the manuscript. Since the patient had no respiratory symptoms, the lung fields showed nothing remarkable, and respiratory function tests were normal, bronchoscopy was not carried out.

2) The patient had no environmental and occupational history of beryllium or other metal exposure. This description was added in the revised manuscript.

3) Possibility of infectious diseases was ruled out. The patient showed negative results of serologic tests for HIV, EBV, CMV, Chlamydia, Mycoplasma, Toxoplasma and Coxiella brunetii (written in the revised manuscript). Other diseases can be denied by the clinical symptoms and pathology of the biopsied lymph node. Bartonella henselae was not examined.

4) The patient had no venereal disease. STS was negative (written in the revised manuscript).

5) Anti-Ro and anti-La were negative (written in the revised manuscript). Anti-neutrophilic cytoplasmic antibodies and AMA were not examined.

6) The patient showed no electrolyte abnormality. Since the hypercalcemia was absent, urinary calcium excretion analysis was not done.

7) Urinalysis showed nothing remarkable (written in the revised manuscript).

8) Immunohistochemical staining as well as Ziehl-Neelsen staining showed negative study for M. tuberculosis as well as acid-fast bacterium. Anti-acid fast bacterium antibody and tuberculin skin test were negative (written in the
manuscript).

9) The diagnostic significance of negative tuberculin skin test was omitted considering advanced age of the patient.

10) In Discussion, we described the etiology of sarcoidosis as follows: Although the exact cause of sarcoidosis is still unknown, the current working hypothesis suggests that it is caused by alteration of immune response after exposure to environmental, occupational or infectious agents in genetically susceptible individuals. Among the infectious agents, mycobacterial and propionibacterial organisms are most commonly implicated as potential etiologic agents. In particular, P. acnes is the only microorganism that has been isolated from sarcoid lesions. All available evidences have suggested the concept that the disease result from an exaggerated Th1 immune responses to specific antigens. In addition, we added the following additional description: Although histologic evidence is mandatory for a definitive diagnosis of sarcoidosis, the histologic findings are not sufficiently specific to make the diagnosis, since non-caseating granulomas are found in a number of infectious diseases. Thus, we excluded the possibility of infectious diseases by applying a number of serologic tests for given diseases. Although P. acnes seems to be a potential etiologic agent, other viral, bacterial and environmental agents and genetic susceptibility might be also involved in the development of sarcoidosis in a complex manner. My colleague, Prof. Y. Eishi, has investigated the etiological relationship between P. acnes infection and sarcoidosis. The related literatures were described in the References.

Please let me know of your decision at your earliest convenience.

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