Author’s response to reviews

Title: Scleritis and anterior uveitis may herald the development of an epibulbar tumor in patients with extranodal Rosai-Dorfman disease: a case report

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Dear Professor Guangde Tu and Reviewers of BMC Ophthalmology:

We thank the members of BMC Ophthalmology for the thoughtful review of our article “Scleritis and anterior uveitis may herald the development of an epibulbar tumor in patients with extranodal Rosai-Dorfman disease: a case report”. We have revised the manuscript based on all of the comments of the reviewers. The revisions are highlighted in red color in the text and are described below in a point-by-point fashion.

Response to Reviewer 1 (Professor Chun-Ju Lin)’s comments:

(1) In "Case presentation" page 5, line 26, the authors mentioned "excessive Demodex mites" in the facial skin biopsy. Could the authors further explain the possible relationship between Rosai-Dorfman disease and Demodex mites?

A: Thank you very much for your recommendations to strengthen our manuscript, and we completely agree with you that there is a possible relationship between Rosai-Dorfman disease and Demodex mites. Demodex mites parasitize healthy skin. Overgrowth of Demodex is found in rosacea patients, and it is speculated that Demodex mites trigger the host immune response by the activation of the TLR2 pathway, leading to skin inflammation [Lacey, N., et al., Demodex mites modulate sebocyte immune reaction: possible role in the pathogenesis of rosacea. Br J Dermatol, 2018. 179(2): p. 420-430.]. However, the pathogenesis of Rosai-Dorfman disease
remains unclear. Rosai-Dorfman disease coexists with inflammatory disease in 10% of cases, such as systemic lupus erythematosus, erythematous, idiopathic juvenile arthritis, autoimmune hemolytic anemia [Abla, O., et al., Consensus recommendations for the diagnosis and clinical management of Rosai-Dorfman-Destombes disease. Blood, 2018. 131(26): p. 2877-2890.]. Therefore, it is theoretically possible that Demodex infestations might play a role in inducing Rosai-Dorfman disease or aggravating the disease. Despite the possible connection between the two disease entities, a literature review did not identify a study analyzing the relationship between Demodex infestations and Rosai-Dorfman disease.

Accordingly, we have revised the manuscript as follows:

P. 8. “It is theoretically possible that Demodex infestations might play a role in inducing RDD or aggravating the disease. Demodex mites parasitize healthy skin. Overgrowth of Demodex are found in rosacea patients, and it is speculated that the Demodex mites trigger the host immune response by the activation of the TLR2 pathway, leading to skin inflammation. RDD coexists with inflammatory disease in 10% of cases, such as systemic lupus erythematosus, erythematous, idiopathic juvenile arthritis, and autoimmune hemolytic anemia. Despite the possible connection between the two disease entities, a literature review did not identify a study analyzing the relationship between Demodex infestations and RDD.”

(2) Was it possible that the immunosuppressive therapy worsened the skin infection of Demodex mites (multiple discrete and confluent papulonodules rapidly evolved over the bilateral cheek, ear and scalp)? What was the rationale that the authors used oral dapsone 100 mg daily for 6 weeks?

A: We completely agree with you that immunosuppressive therapy possibly worsens the Demodex infestations. An in vivo study reveals Demodex mites rapidly colonize genetically modified mice (BALB/c-IL13/IL4) with an impaired Th2 response [Smith, P.C., et al., Demodex musculi Infestation in Genetically Immunomodulated Mice. Comp Med, 2016. 66(4): p. 278-85.]. Thus, if the immunosuppressive therapy causes a shift from a Th2 to a Th1/Th17 immune response, it is possible the number of Demodex will increase. In a study describing dupilumab therapy as the culprit of rosacea, the author speculated that inhibition of the Th2 pathway by dupilumab may induce an overgrowth of Demodex mites and may play a role in the pathogenesis of rosacea [Heibel, H.D., et al., Rosacea Associated with Dupilumab Therapy. J Dermatolog Treat, 2019: p. 1-12.].

Cutaneous Rosai-Dorfman disease can be successfully treated with oral dapsone according to the study by Chan CC et al. [Chan, C.C. and C.Y. Chu, Dapsone as a potential treatment for cutaneous Rosai-Dorfman disease with neutrophilic predominance. Arch Dermatol, 2006. 142(4): p. 428-30.]. Chan demonstrates that numerous neutrophils and histiocytes with a positive myeloperoxidase staining are detected in the specimen obtained from the patients with cutaneous Rosai-Dorfman disease. As in our present case, multiple neutrophils and histiocytes were found in the pathology of the skin biopsy. Because dapsone exerts anti-inflammatory effects through inhibition of myeloperoxidase, which is present in the azurophilic granules of neutrophils, as
As in the lysosomes of monocytes, tissue-resident macrophages and histiocytes, it has become one of the effective treatment options for cutaneous Rosai-Dorfman disease.

Accordingly, we have revised the manuscript as follows,

P.9. “Cutaneous Rosai-Dorfman disease can be successfully treated with oral dapsone according to the study by Chan CC et al. Chan demonstrates that numerous neutrophils and histiocytes with a positive myeloperoxidase staining are detected in specimens obtained from patients with cutaneous Rosai-Dorfman disease. As in our present case, multiple neutrophils and histiocytes were found in the pathology of the skin biopsy. Because dapsone exerts anti-inflammatory effects through inhibition of myeloperoxidase, which is present in the azurophilic granules of neutrophils, as well as in the lysosomes of monocytes, tissue-resident macrophages and histiocytes, it is one of the effective treatment options for cutaneous Rosai-Dorfman disease.”

P. 10. “Immunosuppressive therapy could possibly worsen the Demodex infestations. An in vivo study reveals that Demodex mites rapidly colonize genetically modified mice (BALB/c-IL13/IL4) with an impaired Th2 response. Thus, if the immunosuppressive therapy causes a shift from a Th2 to a Th1/Th17 immune response, it is possible the number of Demodex mites will increase. In a study describing dupilumab therapy as the culprit of rosacea, the author speculated that inhibition of the Th2 pathway by dupilumab may actually induce an overgrowth of Demodex mites and may play a role in the pathogenesis of rosacea.”

(3) The authors might recommend the readers the optimal timing to taper or stop the MTX treatment. What are the key points to make a decision to stop the immunosuppressive therapy?

A: Currently, there is no standard treatment for Rosai-Dorfman disease. The consensus recommends using low-dose methotrexate 20 mg/m2 per week in refractory cases [Abla, O., et al., Consensus recommendations for the diagnosis and clinical management of Rosai-Dorfman-Destombes disease. Blood, 2018. 131(26): p. 2877-2890.]. In our opinion, methotrexate cold be tapered when RDD resolves. Methotrexate could be tapered to 2.5-5 mg per week for 3-6 months as maintenance therapy. Long-term low-dose methotrexate is relatively safe, but blood counts and liver enzymes should be routinely monitored [Visser K et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative Ann Rheum Dis. 2009 Jul;68(7):1086-93. doi: 10.1136/ard.2008.094474. Epub 2008 Nov 25.]

Accordingly, we have revised the manuscript as follows,

P. 9. “The consensus recommends using low-dose methotrexate 20 mg/m2 per week in refractory cases. Based on our experience, methotrexate cold be tapered when RDD resolves. Methotrexate
could be tapered to 2.5-5 mg per week for 3-6 months as maintenance therapy. Long-term low-dose methotrexate is relatively safe, but blood counts and liver enzymes should be routinely monitored.”

Response to Reviewer 2 (Professor Jyotirmay Biswas)’s comments:

(1) Authors reported a case of scleritis and anterior uveitis in patient of epibulbar tumor with extra nodal Rosai Dorfman disease. The case is interesting and rare as the patient is reported with scleritis and anterior uveitis. There is only one case of Rosai-Dorfman disease reported with scleritis of that patient did not have anterior uveitis. The paper needs several grammatical corrections.

A: Thank you very much for your recommendations to strengthen our manuscript, and we feel honored to receive such a positive review. The manuscript has been edited for grammatical corrections by the editors from American Journal Experts, and it was sent for re-editing as you recommended (certificate is provided).

The following is the response to your specific comments in a point-by-point fashion.

(2) The word notorious in Page no:2 line No:11 has to be replaced. It is a non-scientific term.

A: We have changed the word “notorious for” to “characterized by”, and we have revised the manuscript as follows”

P. 2, “…and is characterized by multiple recurrences.”

(3) In Page no: 4 line No: 15 The ocular symptoms somewhat improved is not acceptable. The word somewhat has to be changed.

A: We have deleted “somewhat” as you suggested, and we have revised the manuscript as follows”

P. 4, “Though the ocular symptoms improved, the resolution was incomplete.”

(4) Authors submitted the photograph of scleritis. A slit lamp photograph focusing on anterior uveitis should be provided, as this is case presented with anterior uveitis with scleritis.

A: We completely agree with your concern. A slit lamp photograph focusing on anterior uveitis should be provided, as this was one of the main presenting features. However, a slit lamp with a high-resolution image acquisition system that is able to demonstrate the presence of cells in the
anterior chamber, is not available in our institute. Instead, we described this finding in the manuscript as follows:

P. 4, “The cornea was clear, and 3+ cells were visualized in the left anterior chamber.”