

Successful treatment of Rosai–Dorfman disease using *in situ* photoimmunotherapy

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Abstract

Rosai–Dorfman disease is difficult to cure. *In situ* photoimmunotherapy combines local photothermal therapy with immunoadjuvant. In the present case report, a 39-year-old Chinese man with Rosai–Dorfman disease lesions below the left nostril and left preauricular region was treated with *in situ* photoimmunotherapy. The patient was treated with daily application of topical imiquimod (5%) and laser irradiations every 2 weeks for 8 weeks. After three cycles of treatment, the lesions improved markedly without adverse effects. Our results showed that *in situ* photoimmunotherapy can be used as an effective treatment for Rosai–Dorfman disease.

Key words: Imiquimod, *in situ* photoimmunotherapy, photothermal therapy, Rosai–Dorfman disease

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Introduction

Rosai–Dorfman disease, commonly termed as sinus histiocytosis with massive lymphadenopathy, is typically characterized by fever, painless cervical lymphadenopathy, polyclonal gammopathy and immunologic dysfunction. Extranodal involvement, especially the skin, has been reported in more than 40% of patients with Rosai–Dorfman disease. Symptomatic disease is usually treated with surgery or systemic prednisone.¹ However, these treatment methods seem to be associated with local recurrence and long-term toxicity.

In situ photoimmunotherapy, a form of combination laser immunotherapy and toll-like receptor agonist stimulation, is a tumor-directed immunotherapy technique, in which an intense local immune response is triggered within and around a preexisting deposit of tumor such as a metastasis. It uses near-infrared laser energy to induce increased temperature in target tissue, kill tumor cells directly and release tumor antigens for the generation of antitumor immunity to treat late-stage metastatic cancers.²

In this study, we used *in situ* photoimmunotherapy for the first time to treat a patient with a large, persistent, Rosai–Dorfman disease refractory to other therapies.

Case Report

A 39-year-old man presented with a 9-month history of slowly growing red and raised lesion below the left nostril and left preauricular region [Figure 1a and b]. Associated symptoms such as fever, pain and itching were not reported. On clinical examination, erythematous plaques of 3 cm × 3 cm size was noted on the left cheek and 0.5 cm × 1 cm on the left preauricular region. There was no lymphadenopathy. Laboratory tests including complete blood count, urinalysis, liver function tests, thyroid function test and erythrocyte sedimentation rate were all within normal range. Hepatitis B surface antigen was positive, but rapid plasma reagin and a rapid human immunodeficiency virus antibody test were

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How to cite this article: Li M, Shi L, Luo M, Chen J, Wang B, Zhang F, *et al.* Successful treatment of Rosai–Dorfman disease using *in situ* photoimmunotherapy. *Indian J Dermatol Venereol Leprol* 2017;83:332-6.

Received: April, 2016. **Accepted:** November, 2016.

Access this article online	
Quick Response Code:	Website: www.ijdv1.com
	DOI: 10.4103/ijdv1.IJDVL_356_16



Figure 1a: Erythematous plaque below the left nostril before treatment



Figure 1b: Erythematous plaque over the left pre-auricular region before treatment

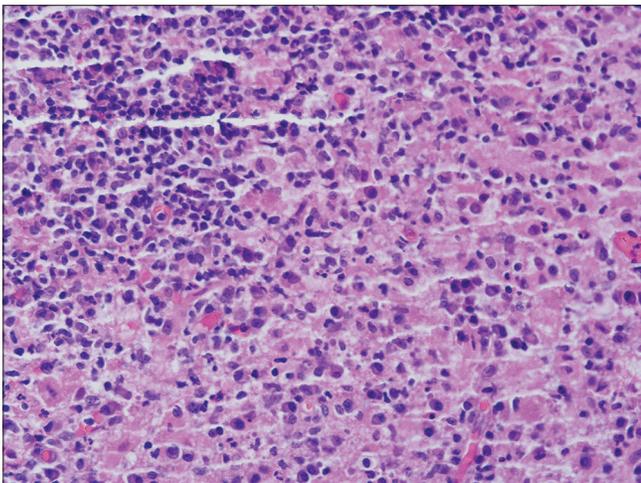


Figure 2: Dermal inflammatory infiltrate consisting of a large number of histiocytes, plasma cells and lymphocytes cells (H and E, ×400)

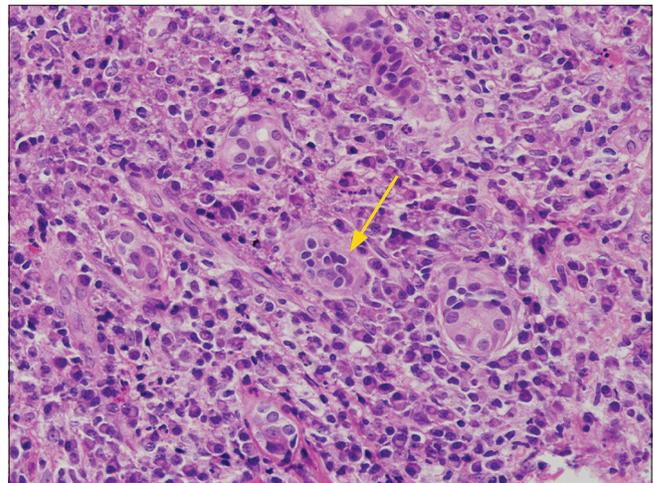


Figure 3: The histiocytes showing emperipolesis (H and E, ×400)

negative. An incisional biopsy from the lesion below the left nostril was taken which showed a nodular infiltration within the dermis consisting of plasma cells, lymphocytes and histiocyte aggregates [Figure 2]. In addition, emperipolesis found large histiocytes [Figure 3]. Immunohistochemistry was positive for S-100 [Figure 4a] and CD68 [Figure 4b], but negative for CD1a [Figure 4c]. The positive rate of Ki-67 was 5% [Figure 4d]. Based on these findings, a diagnosis of Rosai–Dorfman disease was made.

According to the clinical manifestations, the patient was initially treated with oral thalidomide 100 mg *bis in die*. However, after treatment for 2 months, the lesion was not improved significantly. Instead, the patient developed peripheral neuropathy and gastrointestinal side effects. Therefore, thalidomide treatment was stopped. The patient refused surgery and steroids, due to the known adverse effects. Hence, he was referred for consideration of treatment with *in situ* photoimmunotherapy. One cycle of *in situ* photoimmunotherapy included daily application of 5% imiquimod (Sichuan Med-Shine Pharmaceutical Co. Ltd.,

China) and irradiation of the lesions with 808-nm diode laser (power density = 2.0 W/cm², spot size = 2 cm², applied for 10 min/treatment spot) at 2-week intervals for 8 weeks [Figure 5]. The patient received three cycles of treatment at an interval of 4 weeks. During irradiation of the lesion, the temperature of the skin surface was recorded by an infrared thermal imager (FLIR Systems, Inc., USA, T420-NIST). A thermal gradient on the skin surface was generated and the highest temperature reached was 43.4°C [Figure 6]. After three cycles of *in situ* photoimmunotherapy, the patient's condition became better. Ultimately, the lesions were flat [Figure 7a and 7b]. After completion of the third cycle, the patient was followed up once a month. No adverse effects and recurrence were seen during the follow-up of 6 months.

Discussion

As Rosai–Dorfman disease is known to have spontaneous regression, aggressive therapeutic measures are not recommended.² The present review found that spontaneous resolution (partial or complete) occurred in 16.1% of cases.³ Available therapeutic measures such as surgery and steroids are associated with adverse

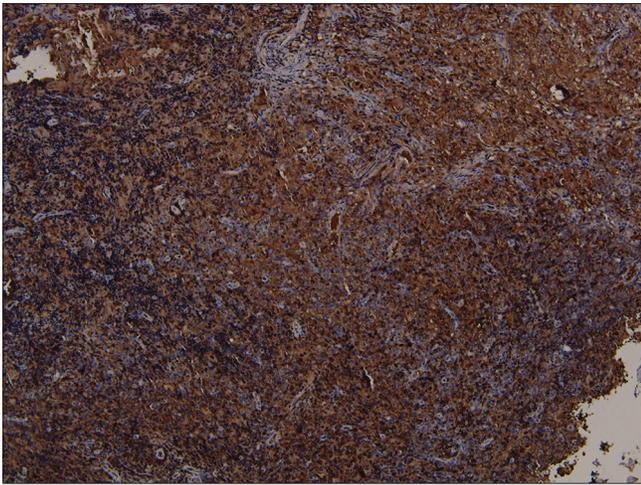


Figure 4a: The histiocytes showing positive for S-100 (×400)

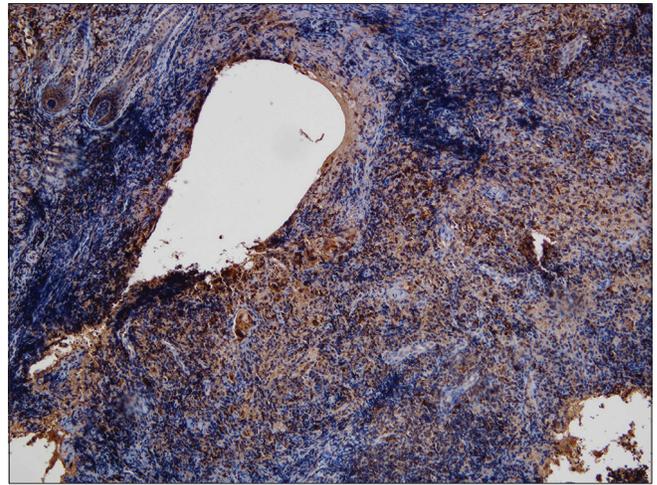


Figure 4b: The histiocytes showing positive for CD68 (×400)

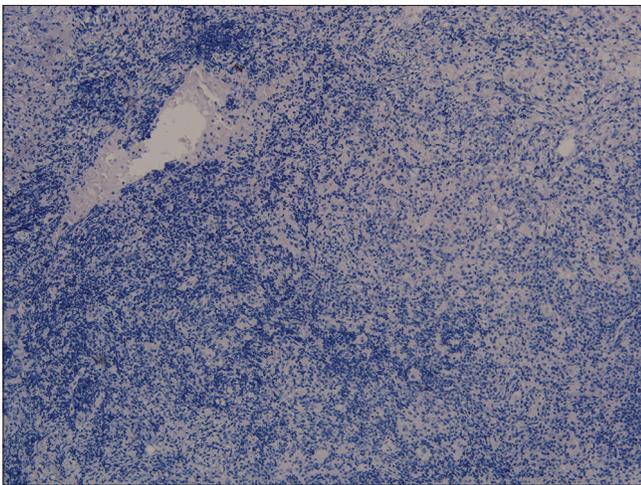


Figure 4c: The histiocytes showing negative for CD1a (×400)

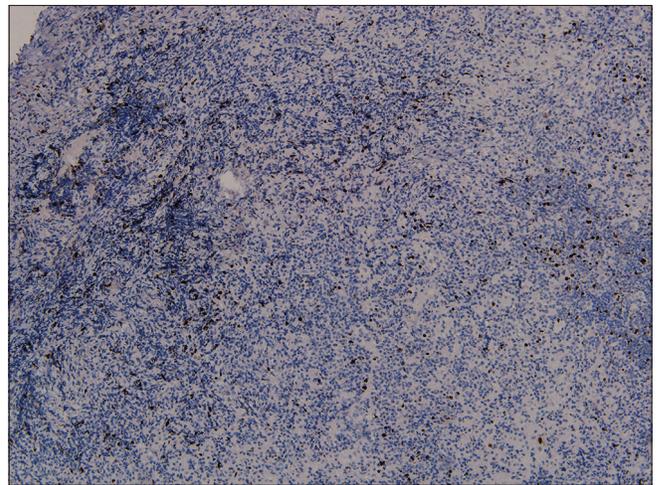


Figure 4d: The histiocytes showing negative for Ki-67 (×400)

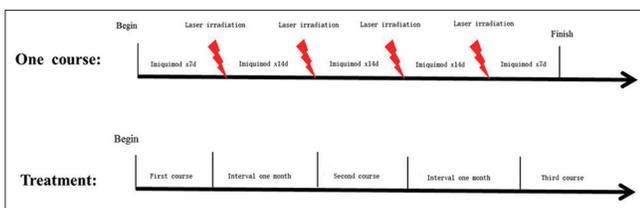


Figure 5: Treatment cycle of photothermal immunotherapy for RDD patient. Three courses of treatment were carried out until the response to the treatment was complete

effects.⁴ Localized Rosai–Dorfman disease can be treated with complete surgical resection, but it has a risk of local recurrence.⁵ Furthermore, cosmetic appearance might represent a therapeutic challenge for surgery. Moreover, due to fear and expense of surgery, many patients refuse the treatment. On the other hand, typical initial steroid treatment requires a high dose to achieve successful results. Most of the patients achieve a quick remission with a reduction of inflammatory markers and size of cervical lymph nodes. Unfortunately, steroid tapering was seen to result in reoccurrence of Rosai–Dorfman disease. During every recrudescence, patients experienced long-term toxicity with steroids, such as increased lymph nodes and an increase in inflammatory markers.

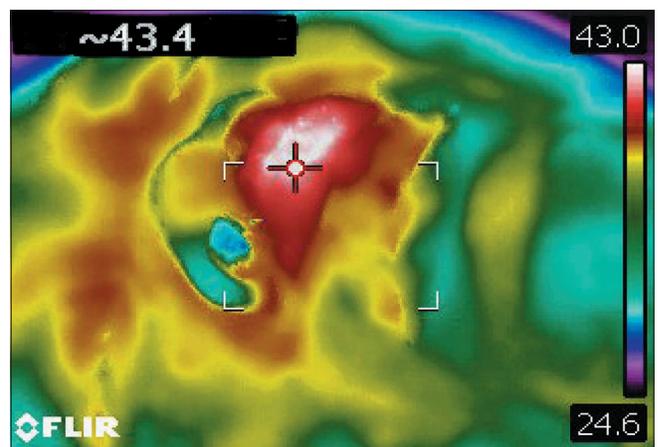


Figure 6: Thermal image taken by an infrared thermal imager, showing a thermal gradient with the highest temperature of 43.4°C on the surface

In situ photoimmunotherapy is considered a novel treatment for cancer. Wei R. Chen *et al.* reported that 11 late-stage melanoma patients received *in situ* photoimmunotherapy in one or multiple 6-week treatment cycles. The probability of 12-month overall



Figure 7a: After the three courses of treatment, the lesions below left nostril were flat and remarkably improved

survival was 70%. Here, we report for the first time the use of *in situ* photoimmunotherapy to treat Rosai–Dorfman disease. This report shows palliative responses to *in situ* photoimmunotherapy for patients who have refractory Rosai–Dorfman disease. As we all know, *in situ* photoimmunotherapy consists of photothermal therapy and toll-like receptor agonist stimulation has been shown to cure some solid tissues.⁶ This is because of the synergistic effects of photothermal therapy and imiquimod. Two mechanisms of action of *in situ* photoimmunotherapy in Rosai–Dorfman disease can be postulated: One, *In situ* photoimmunotherapy uses near-infrared laser energy to induce increased temperature in target tissue, kill cells directly and release tumor antigens to generate antitumor immunity.⁷ Antigen-presenting cells gather these antigens and migrate to lymph nodes. Dendritic cells present the antigens to T-cells that can induce immune responses against cells.⁶ On microscopic examination of Rosai–Dorfman disease, the involved lymph nodes are altered by sinusoidal dilation which contains lymphocytes, histiocytes and plasma cells.² Two, Rosai–Dorfman disease is associated with high levels of tumor necrosis factor- α and interleukin-6;⁸ imiquimod⁹ also induced IL-1 α , IL-1 receptor antagonist, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte CSF (G-CSF), and macrophage inflammatory protein-1 α to enhance therapeutic effect.

We report the possible mechanisms of action of *in situ* photoimmunotherapy for Rosai–Dorfman disease and also report that *in situ* photoimmunotherapy has no obvious side effects. In our case, the patient had a 9-month history of Rosai–Dorfman disease and there was no improvement in the skin lesions through a variety of methods. Our patient with Rosai–Dorfman disease achieved improvement gradually as the *in situ* photoimmunotherapy cycles increased, so we believe that the improvement is due to three cycles of *in situ* photoimmunotherapy



Figure 7b: After the three courses of treatment, the lesions over the left preauricular region were flat and showed remarkable improvement

treatment. *In situ* photoimmunotherapy may be an appropriate therapy in refractory disease, owing to facial and other special parts to protect the appearance. The present study is the first reported case of *in situ* photoimmunotherapy inducing remission in Rosai–Dorfman disease. Because this case is only a case report, we will expand the case series and perform randomized controlled trials to further verify the efficacy of *in situ* photoimmunotherapy in the treatment of Rosai–Dorfman disease.

Conclusion

ISPI can be used as an effective treatment for Rosai–Dorfman disease.

Financial support and sponsorship

This study was supported financially by the National Natural Science Foundation of China (81272990, 81472538, 81472796).

Conflicts of interest

There are no conflicts of interest.

Ethics statement

The current study was approved by Shanghai Skin Disease Hospital.

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