Cutaneous Rosai-Dorfman Disease: A Case Report of Rare Presentation of Rosai-Dorfman Disease

Jidapa Arpornpattanapong MD,
Walaiorn Pratchyapruit MD,
Poonnawis Sudtikoonaseth MD,
Pimpa Tantanasrigul MD.

ABSTRACT:

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INSTITUTE OF DERMATOLOGY, MINISTRY OF PUBLIC HEALTH, BANGKOK, THAILAND.

Rosai-Dorfman disease (RDD) or sinus histiocytosis with massive lymphadenopathy, is a rare benign non-Langerhans cell histiocytosis characterized by proliferation of activated histiocytes within the affected tissues. Massive, painless lymphadenopathy is a classic presentation, usually affected male children and young adults. Extranodal involvement is reported in some cases. Isolated cutaneous involvement is very rare. We report a 48-year old Thai male presented with multiple, non-scaly erythematous to yellowish papules and plaques on the face for 17 months without lymphadenopathy. Histopathology showed dense infiltration of histiocytes, lymphocytes and plasma cells in dermis with emperipolesis phenomenon. Immunohistochemistry demonstrated positive S100 protein and weakly positive CD68. The clinical presentation and histopathological results were compatible with cutaneous Rosai-Dorfman disease.

Key words: Rosai-dorfman disease, sinus histiocytosis with massive lymphadenopathy, cutaneous rosai-dorfman disease

From: Institute of Dermatology, Department of Medical Services, Ministry of Public Health, Bangkok, Thailand.
Corresponding author: Walaiorn Pratchyapruit MD., email: walaiornp@hotmail.com

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Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a rare non-Langerhans cell histiocytosis, first described in 1965 by Destombes[1] and first defined in 1969 by Rosai and Dorfman[2]. It is characterized by presenting of activated histiocytes accumulating within the affected tissues. The classic presentation of RDD is massive, painless lymphadenopathy with extranodal involvement in 43% of cases[3]. The isolated cutaneous form is rare. The majority of patients have an indolent clinical course with spontaneous regression. We reported a rare case of cutaneous RDD which refractory to the treatment.

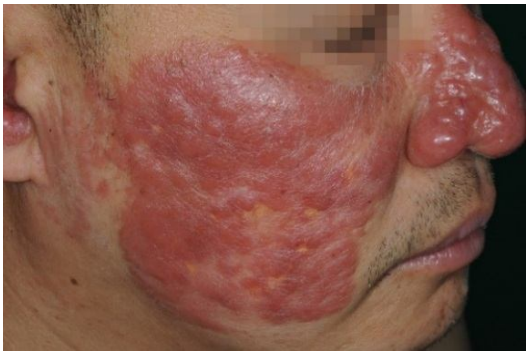

Figure 1 Multiple well-defined, non-scaly erythematous to yellowish papules and plaques at both cheeks, nose, forehead and right ear pinna

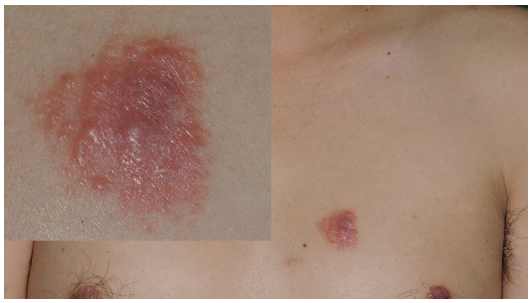

Figure 2 Well-defined, non-scaly erythematous papules and plaques on the upper chest

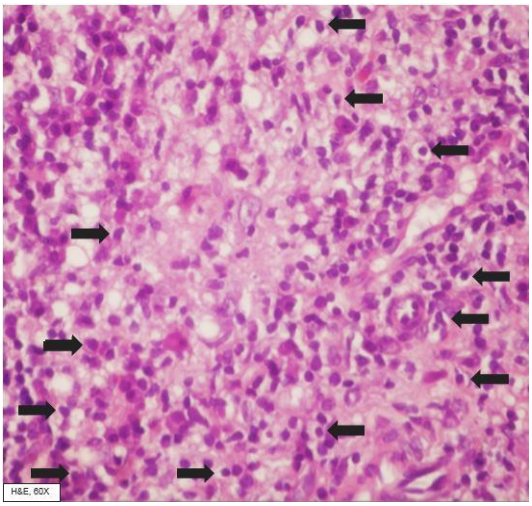

Figure 3 Dense infiltration of mixed inflammatory cells in dermis consisted of large histiocytes, lymphocytes, plasma cells. Emperipolesis phenomenon, engulfment of inflammatory cells by histiocytes that express S100, is remarkable.

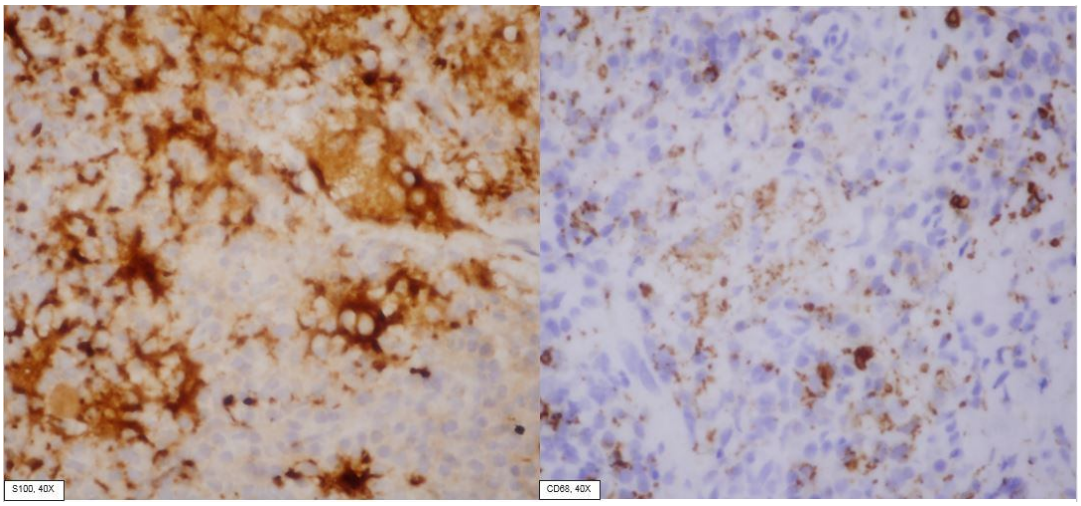

Figure 4 A) shows S100 positive histiocytes B) shows weakly positive CD68

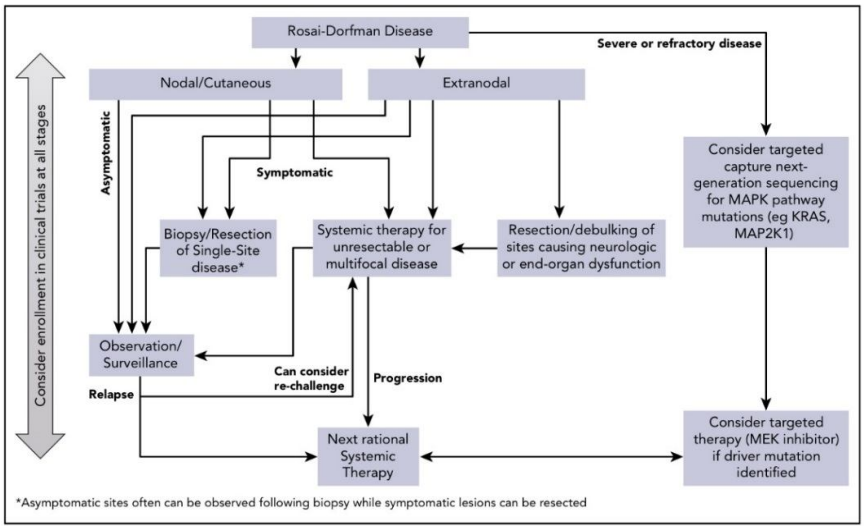

Figure 5 A proposed management algorithm for patient with RDD, by The American Society of Hematology[6]

Case report

A 48-year-old Thai male patient from Bangkok, presented with a 17-month history of slowly progressive, non-pruritic, red plaques on the face (Figure 1). After 2 months of the rash onset, he underwent a skin biopsy at a university hospital, which showed mixed cell granuloma in the dermis. The laboratory investigations for fungal, mycobacterial infection and antinuclear antibody were negative, only mild elevated erythrocyte

sedimentation rate was found. He was diagnosed with granulomatous rosacea. Despite 16 months of various treatments including doxycycline, short-course prednisolone, isotretinoin, intralesional corticosteroids, topical metronidazole, and topical azelaic acid, the lesion gradually enlarged and extended over the forehead, right ear pinna, and chest. The patient sought a second opinion at The Institute of Dermatology, Bangkok, where his condition was reviewed. He never experienced systemic symptoms of Rosai-Dorfman disease such as abnormal lumps at any parts of the body, history of fever, night sweat or significant weight loss. He denied a history of hematologic disorders, autoimmune diseases, as well as the history of taking any oral medications, herbs, or other supplements before the onset of the lesion. There was no family history of the same clinical presentation. Physical examination showed normal vital signs. No signs of anemia, no lymphadenopathy or hepatosplenomegaly was observed. The dermatological examination demonstrated multiple non-scaly erythematous to yellowish indurated papules and plaques at both cheeks, nose, forehead, right ear pinna, and upper chest (Figure 2). Oral ulcer, hair, and nail abnormality were absent. A skin biopsy was repeated at the nose and revealed dense infiltration of mixed inflammatory cells in the dermis consisted of lymphocytes, plasma cells, and large histiocytes with abundant pale cytoplasm. Engulfed intact inflammatory cells in the cytoplasm of the large histiocytes or emperipolesis phenomenon is remarkable (Figure 3). Immunohistochemical staining of the histiocytes showed a positive stain for S100 and a weakly positive stain for CD68 (Figure 4). CD1a and Langerin staining were not performed. Tissue direct immunofluorescence, slit-skin smear for *M. leprae*, Acid Fast stain AFB, Periodic Acid Schiff stainPAS, Gomori methenamine silverMS staining, polymerase chain reaction PCR, and culture for mycobacterium were negative. Laboratory investigations including complete blood count, chest x-ray, renal, and liver function tests were also done without remarkable results. The diagnosis of cutaneous Rosai-Dorfman disease was established. The patient initially received methotrexate 15 mg/week for 24 weeks, which resulted in a partial response. However, the remaining facial lesions appeared unsatisfied so he was referred to a hematologist for chemotherapy administration. Prior to receiving the medication, he underwent chest and abdominal CT computerized tomography scan (with contrast) to evaluate the systemic involvement of the disease. The results showed neither internal lymph node nor internal organ involvement.

Discussion

The onset of RDD is more frequently found in young adults and children, although it also reported in patients up to 74-year-old. It is more common in African population, while the cutaneous form is more common in Asians[4]. The pathogenesis of RDD is unclear. Previous studies postulated viral infections as one of the associations such as human herpes virus, Epstein-Barr virus, parvovirus B19, polyomavirus, cytomegalovirus, and HIV[5]. Genetic predisposing is proven as another etiology of RDD, as germline mutation of the *SLC29A3* gene is reported in familial form RDD. Recent studies also confirmed *KRAS*, *MAP2K1*, *NRAS*, and *ARAF* somatic mutations in the lesional tissue of RDD subjects[6].

RDD patients presented with various clinical presentations. In classic form, massive, painless, bilateral cervical lymphadenopathy are characteristic features, although any site of lymph nodes and the extranodal sites can be affected including orbits and eyelids (11%)[3], skin and soft tissue (10%)[7], bone (5-10%), kidney (4%), central nervous system (<5%), intrathoracic (2%) and gastrointestinal tract (<1%)[6]. Cutaneous involvement, on the other hand, can be a sole manifestation but is very rare. The characteristic skin lesions are erythematous to xanthomatous or red-brown macules, papules, nodules, or plaques. The face is the most commonly affected site, followed by the back, chest, flank, and shoulder, respectively. Other presentations such as pustules, acneiform lesion, vasculitis-mimicking lesion, or panniculitis are rare[8]. Despite the benign nature of the disease, 10% of patients were associated with autoimmune disorder[3] such as systemic lupus erythematosus, rheumatoid arthritis, and idiopathic juvenile arthritis. Hodgkin lymphoma, non-Hodgkin lymphoma, and other histiocytosis are also reported. Moreover, the increasing of IgG4-positive plasma cells in RDD patients with lungs, liver, and colonic involvement might suggest a possible association of these two disorders[9]. However, due to the financial issue, the investigation for IgG4/IgG ratio was not done in our patient.

The histopathology of RDD lesional tissue demonstrated large histiocytes with pale cytoplasm admixed with inflammatory cells infiltration, i.e., lymphocytes, plasma cell, and occasionally eosinophils. Emperipolesis, characteristic but not pathognomonic of RDD, is helpful in the diagnosis. However, extranodal tissue, including skin, often showed a higher degree of fibrosis and is usually more difficult to identified emperipolesis. To highlight the activated histiocytes in such lesions, immunohistochemical staining is required. Positive for S100 and fascin, variable CD68 positivity but negative for Langerin (CD207) and CD1a help in diagnosis. However, the emperipolesis might not always present in early

disease as in our case. Thus, mindful follow-up and re-biopsy might be required, while the clinical correlations are always necessary[10].

Previously, there is no treatment guideline available for RDD due to disease rareness and lack of clinical trial. Later, in 2018, The American Society of Hematology published a consensus recommendation for diagnosis and management of Rosai-Dorfman-Destombes disease. Non-pharmacological management consists of observation, which results in 20-50% remission of patients with cutaneous or nodal involvement. Surgical removal of the unifocal lesion or debulking of the large lesion is also mentioned. Another option is radiotherapy in refractory disease or patients with contraindication for systemic therapy. The pharmacological treatment consists of various modalities including corticosteroids (systemic form and intralesional form) and immunomodulatory agents (thalidomide, lenalidomide, azathioprine, imatinib, and rituximab). Chemotherapy (methotrexate, 6-mercaptopurine, vinca alkaloids, cladribine, and combination regimens) are effective in some refractory cases. Other novel drugs such as cobimetinib and clofarabine are undergoing clinical trials. A proposed management algorithm is shown in Figure 5[4]. The prognosis of cases with multifocal and extranodal disease especially liver, renal or lower respiratory tract involvement seems unfavorable[3].

In conclusion, cutaneous involvement can be the only presentation of RDD, thus, patients who have clinical presentations compatible with RDD should be mindful about the diagnosis. The histopathology which demonstrates emperipolesis and characteristic immunohistochemistry are also helpful. These hallmark features may not be promptly identified in the early disease. Therefore, long term follow-up and serial biopsy might be necessary. Last but not least, despite the spontaneous regression of most patients, some cases had protracted clinical course and required advanced treatment as our patient required.

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