Abstract. Rosai-Dorfman disease (RDD), or sinus histiocytosis with massive lymphadenopathy, commonly involves the lymph nodes but may secondarily involve the skin. Purely cutaneous disease without lymphatics or internal organ involvement occurs rarely. The present report detailed a rare case of 18F-fluoro-2-deoxyglucose positron emission-computed tomography (18FDG PET-CT) performed in a 33-year-old male soldier with a purely cutaneous form of RDD. Staging with 18FDG PET-CT was ordered prior to excisional biopsies of the aforedescribed masses and pathology reported RDD. The case demonstrated accurate localization of increased radioglucose metabolism. The present case was also discussed in light of literature data in terms of clinical features, etiologies, histology, medical imaging, therapy planning and prognosis.

Introduction

Rosai-Dorfman disease (RDD), or sinus histiocytosis with massive lymphadenopathy, is a relatively rare self-limited benign disease (1,2). This atypical cellular disorder was described by Pierre-Paul Louis Lucien Destombes for the first time in 1965 and was labeled as a distinct pathological entity by Rosai and Dorfman in 1969 (2). Although RDD predominantly affects children <10 years of age (66% of cases) and young adults <20 years old (80% of cases) with male predilection, cutaneous disease is also encountered in women in their fourth decade (3). The systemic form of RDD is commonly observed in African-American individuals, whereas the purely cutaneous form is more common in Asian and Caucasian ethnicities (4). The etiology of RDD is unknown; possible causes may be viral infections (including Epstein-Barr virus, parvovirus B19 and human herpes virus), immunodeficiency, autoimmune disease and neoplastic processes (5,6). The clinical course of RDD is often benign, though lethal outcomes are also possible when multiple organs are involved (7). The treatment strategies may be different according to the severity or vital organ involvement (8). In patients with RDD requiring systemic treatment, steroids are a first-line therapeutic option that produce responses in nodal and extranodal disease. Radiation may be used as a palliative option for symptomatic disease. Surgery is an appropriate option for disease that may be excised, such as primary central nervous system involvement. In cases of disseminated RDD or those refractory to surgery, radiotherapy or steroids, chemotherapy has been used with varying degrees of success (9). Clinical outcome depends on the affected organs, as well as the number of extranodal sites involved (10).

The present report described a rare case of 18F-fluoro-2-deoxyglucose positron emission-computed tomography (18FDG PET-CT) performed in a young adult male with a rare purely cutaneous form of RDD.

Case report

A 33-year-old male soldier, previously healthy, presented to dermatology clinics of the Central Military Hospital (Beirut, Lebanon) in June 2014 for evaluation of two new onset subcutaneous enlarged and asymptomatic masses located along the left cheek and the right upper gluteal region. On physical examination, masses were firm with overlying indurated skin, non-tender and painless. Extensive biological test results, including complete blood count, platelet count, erythrocyte sedimentation rate, C-reactive protein, complement component 3, complement component 4, rheumatoid factor and lactate dehydrogenase, were unremarkable. According to their tumor feature, and as cutaneous lymphoma was considered as a differential diagnosis, staging with 18FDG PET-CT was ordered prior to excisional biopsies of the aforedescribed masses, and pathology reported RDD.
HADCHI ET AL: CUTANEOUS ROSAI-DORFMAN DISEASE: A CASE REPORT

A total body $^{18}$FDG PET-CT scan was obtained for staging purposes and to guide therapy initiation. Cheek and gluteal masses were of irregular contours with equivalent metabolic level of radioglucose (Fig. 1). They measured 55x24 mm and 70x32 mm in size, respectively, with a standardized uptake value average of 4 and 4.2, respectively, and a standardized uptake value maximum ($SUV_{max}$) of 8.9 and 9, respectively. Initially, no evidence of active lymph node involvement was noted on both sides of the diaphragm nor other cutaneous or extranodal active sites.

Microscopy of excisional biopsy demonstrated dermal inflammatory infiltrate, essentially macrophages with large cytoplasm, vesicular nuclei and evident nucleoli. On immunohistochemistry, the large pale macrophages demonstrated strong, diffuse cytoplasmic and nuclear staining for S100 protein, with focal and less intense staining for cluster of differentiation (CD) 68 (histiocytic marker). The cells were negative for CD1a, A1K protein, vimentin and smooth muscle actin. Of note was the recognition of non-staining of lymphocytes in proximity to the macrophages, suggesting intracytoplasmic phagocytosis.

A conservative approach (clinical observation) was chosen following surgical excision, and an 8-month $^{18}$FDG PET-CT follow-up demonstrated no evidence of local recurrence or new abnormal focal uptake in the rest of the body (Fig. 2). However, 18 months later, a local recurrence of the major RDD mass of the gluteal region was suspected on dermatological examination, with the interval appearance of one paratracheal active lymph node (diameter, 22 mm; $SUV_{max}$, 9.3). The surgical bed of the left cheek RDD mass remained completely inactive (Fig. 3). The paratracheal lymph node was considered as the nodal part of RDD according to clinical feature progression, and its management did not warrant histological documentation by means of an invasive act of thoracoscopy.

Written informed consent was obtained from the patient for publication of the present case report.

Discussion

The most common symptoms on presentation of RDD are painless cervical lymphadenopathy associated with fever, night sweats and weight loss; other symptoms are related to sites of involvement (11). Lymphatic disease manifests predominantly with bilateral massive cervical adenopathy (12). Neurological disease reveals as intracranial masses and, less frequently, intraspinal dural-based masses (13). RDD may affect the breasts, lungs, gastrointestinal tract and, less often, the bones (12). Involvement of the eyes, nose and trachea have also been described (8). Patients with RDD may present to rheumatologists due to bone or joint pain (14).

Mixed nodal and extranodal involvement is the most common presentation of RDD and the skin is the most common extranodal site affected; however, it is rarely isolated (13). The cutaneous form was first described in 1978 by Thawerani et al (15). Cutaneous RDD is distinct from the systemic form and is confined to the skin without lymphadenopathy and with different dermographic features (16). Skin lesions are often papules or nodules that are firm, indurated.

Figure 1. RDD diagnosis by $^{18}$FDG PET-CT. (A) Baseline whole body three-dimensional $^{18}$FDG PET-CT revealed the two hot spots of hypermetabolism located along the left cheek (red arrow) and the right gluteal region (green arrow), representing the subcutaneous masses of RDD. Axial cross-sections of (B) PET and (C) fused PET-CT of the head/neck revealed the left cheek subcutaneous hypermetabolic mass of RDD (red arrow). Axial cross-sections of (D) PET and (E) fused PET-CT of the pelvis revealed the right gluteal sub-cutaneous hypermetabolic mass of RDD (green arrow). RDD, Rosai-Dorfman disease; $^{18}$FDG PET-CT, $^{18}$F-fluoro-2-deoxyglucose positron emission-computed tomography; PET, positron emission tomography; CT, computed tomography.
and ranging in size from 1-10 cm. Pustular, psoriasiform and acneiform presentations have also been documented (17). Cutaneous RDD has a benign course usually with spontaneous regression in the majority of cases (9). Therapy may be required for relapsed cases and for cosmetic reasons only.

The present report detailed a rare case of cutaneous RDD, isolated initially and presenting as bifocal cutaneous/subcutaneous masses involving the left cheek and right gluteal region. The dermatologic pattern of the subcutaneous firm masses with overlying skin indurated violaceous plaque has previ-
ously been described in the literature (18). The two masses in the present case of RDD measured >5 cm in diameter and were likely present for several years.

RDD was previously defined by the accumulation of histiocyes that do not meet the phenotypic criteria for the diagnosis of Langerhans cells (19,20). A recent classification of histiocytic disorders and neoplasms of the macrophage-dendritic cell lineage has been proposed with RDD forming its own subtype (R group) due to its unique characteristics (21). In this more recent classification, histiocyte proliferation is presumably reactive and polyclonal (22). The diagnosis requires the presence of large histiocytic cells displaying hypochromatic nuclei and pale cytoplasm, often with abundant emperiplois with positive immunohistological staining for S100, fascin, CD68, CD14, human leukocyte antigen-antigen D related and CD163. Typically, negative staining for CD1a and CD207 distinguishes it from Langerhans histiocytosis (22).

In lymph nodes, the large S100-positive histiocytes are predominantly localized within the sinuses, and the cortex often contains numerous plasma cells and activated B cells (21). The cutaneous lesions are characterized by proliferation of polygonal S100-positive histiocytes and mixed inflammatory infiltrates (23) that are composed predominantly of epithelioid histiocytes with a pale to eosinophilic cytoplasm as Russell bodies (2). The pathognomonic RDD cells demonstrate abundant granular and palely eosinophilic cytoplasm with feathery borders and medium nuclei (24). However, the most important feature is phagocytosis of intact lymphocytes, plasma cells and polymorphonuclear leukocytes within the cytoplasm, a process termed as emperiploes or lymphophagocytosis (24).

In the present case, the histological diagnosis of RDD evoked on soft tissue, skin and deep margin excisions, was based on the strong histiocyte expression of S100 marker. Furthermore, the recognition of non-staining lymphocytes in proximity to the macrophages suggested emperiploes. Langerhans's cell histiocytosis, Erdheim-Chester disease and inflammatory myofibroblastic tumor were considered in the differential diagnoses list; however, the immunostaining profile was not supportive of any of these considerations.

RDD usually affects multiple nodal and extranodal sites with variable radiological aspect on imaging studies, commonly affecting the head and neck areas. On ultrasound, nodal disease appears as multiple large, round, well-defined hypoechoic nodes, with loss of echogenicity in the hilum (12). On contrast-enhanced CT scan, it appears as homogenously enhancing lymph nodes and, in some cases, as hypodense owing to cystic changes (12). On gadolinium-enhanced magnetic resonance imaging (MRI), lymph nodes are hypointense on T1- and T2-weighted images, and homogeneously enhancing following gadolinium administration (12). In such cases, the main radiological differential diagnoses would be non-Hodgkin lymphoma, reactive lymph nodes, tuberculous adenopathies, Langerhans histiocytosis or Castleman disease (25).

Skin RDD appears on ultrasounds as ill-defined, hypoechoic cutaneous and subcutaneous nodules (26). On CT scans, it appears as ill-defined enhancing lesions of the skin, while on gadolinium-enhanced MRI scans, lesions are hypointense on T1-weighted MRI, hypointense to hyperintense on T2-weighted MRI relative to underlying muscle, and homogeneously enhancing following gadolinium administration (12).

Similar to various benign or malignant lymphoproliferative disorders, nodal and extranodal RDD lesions have been demonstrated to be 18FDG-avid (27-30). This avidity is attributed to the high level of the radioglucose metabolism of the proliferating histiocytes as well as the infiltrating inflammatory cells (27-30). Various studies have reported the utility of 18FDG PET-CT for monitoring steroid therapy, particularly in the visceral form of the disease (29,31). 18FDG PET-CT is also the method of choice for staging and follow-up on treatment response in extranodal disease (29). Multiple and various case reports that diagnosed or managed diseases according to 18FDG PET-CT follow-up scans are available in literature. Notably, a case report of RDD mimicking a lymphoma on 18FDG PET-CT in a pediatric patient demonstrated that the exact diagnosis was only made following histological sampling (32). Additionally, a case of a hypothalamic lesion with 18FDG-avidity was diagnosed as RDD of the central nervous system (CNS) (33). Follow-up on treatment responses using 18FDG PET-CT have also been described for a gastrointestinal case presenting as Crohn's disease of ileum, for a case of local and isolated CNS relapse following neurosurgery of a primary RDD of the brain (34), and a case of bone involvement by RDD (28). In a rare case report, the 18FDG PET-CT demonstrated abnormal hyperactivities limited to the spleen and the liver, without active lymphadenopathy, and was used to indicate the splenectomy alone, as both a diagnostic and therapeutic approach (30).

In the present case, the first 18FDG PET-CT examination demonstrated initially the only cutaneous form of RDD, which is a rare finding previously described in a single case report by Huang et al (35). It demonstrated high and equivalent metabolic activity of radioglucose in the cheek and gluteal cutaneous masses, which shared similar histology in the present case. 18FDG PET-CT results were a prerequisite based on which the therapeutic strategy was planned. As no nodal or systemic disease was associated initially with the two sites of cutaneous lesions, they were excised surgically and no medical treatment was offered. The first recurrence was local in the surgical bed of the major lesion affecting the right gluteal region, which was re-excised, with the interval appearance of hypermetabolic paratracheal lymph node. Therefore, findings prompted steroid initiation. The right gluteal mass relapsed again, and was suspected on dermatological examination and confirmed by 18FDG PET-CT criteria. The elevated metabolic activity recorded in the present case of cutaneous lesions (SUVmax, 9) may have represented an aggressive nature, which would explain the local relapses following surgical excisions. The cutaneous mass of the left cheek was less voluminous than the right gluteus one, and did not locally relapse, indicating that surgery was successful at fully removing the mass. Therefore, the present case highlighted the importance of 18FDG PET-CT scanning in staging and decision making or therapeutic recommendations.

Prognosis of RDD is variable with a large spectrum, starting with spontaneous healing within weeks to months, and finishing at the other end with persistence or recurrence following surgical excision or medical treatments (36). Often, RDD regresses spontaneously and aggressive therapeutic
measures are not recommended (36). When the disease progression affects the kidneys, the lower respiratory tract, the pancreas or the liver, during its long-term clinical course with remissions and exacerbations, end organ damage may occur and may have a fatal outcome (2).

Localized RDD of skin may be treated with complete surgical resection, with a risk of local recurrence (37). It is important to note that the cosmetic appearance of skin represents a therapeutic challenge for surgery. Recently, a study by Li et al (38) reported the possible mechanisms of action of in situ photoimmunotherapy for RDD, which demonstrated no obvious side effects (38).

Surgical excision is also considered when vital organs or vascular/neurological compromise is imminent, but also for cosmetic reasons when the skin is involved (39). Otherwise, conservative approaches and regular follow-up is preferred. Radiotherapy, chemotherapy or steroids may lead to a transient response; however, they do not provide long-term benefits (2). Surgery and steroid therapy are associated with adverse effects (40).

In the present case, the disease was initially limited to the skin, and the initial treatment was a surgical excision. Follow-up 18F-FDG PET-CT was performed three times over a 2-year period, and it documented a complete response following the initial surgical excision of the cutaneous lesions. Local recurrences in the skin treated surgically, and an interval appearance of a paratracheal lymph adenopathy, which required systemic therapy.

In conclusion, to the best of our knowledge, there is only one prior case of a cutaneous-only form of RDD diagnosed by 18F-FDG PET-CT scan in English literature (35). Therefore, the present report described the second case of isolated cutaneous RDD evaluated by 18F-FDG PET-CT scan, which displayed high radioglucose metabolism. The present case demonstrated the importance of 18F-FDG PET-CT imaging in the screening of extranodal RDD, even with cutaneous involvement. In the latter case, 18F-FDG-avidity is usually attributed to the infiltrative and inflammatory changes caused by the disease process. Ultimately, this imaging modality may aid with making therapeutic recommendations.

References

1. Rosai J and Dorfman RF: Sinus histiocytosis with massive lymphadenopathy. A newly recognized benign clinicopathological entity. Arch Pathol 87: 63-70, 1969.
2. Foucar E, Rosai J and Dorfman R: Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): Review of the entity. Semin Diagn Pathol 7: 19-73, 1990.
3. Chappell JA, Burkemper NM, Frater JL and Hurley MY: Cutaneous rosai-dorfman disease and morphea: Coincidence or association? Am J Dermatopathol 31: 487-489, 2009.
4. Brenn T, Calonje E, Granter SR, Leonard N, Grayson W, Fletcher CD and McKee PH: Cutaneous rosai-dorfman disease is a distinct clinical entity. Am J Dermatopathol 24: 385-391, 2002.
5. Pulsoni A, Angelh G, Falucci P, Matera R, Pescarmona E, Ribersani M, Villivì N and Mandelli F: Treatment of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): Report of a case and literature review. Am J Hematol 69: 67-71, 2002.
6. Elbuluk N, Egbers R, Taube JM and Wang TS: Cutaneous Rosai-Dorfman Disease in a Patient with Human Immunodeficiency Virus. Dermatol Online J 22: 13030/4Q216239f3, 2016.
7. Chen J, Tang H, Li B and Xiu Q: Rosai-Dorfman disease of multiple organs, including the epibracium: An unusual case with poor prognosis. Heurli Ung 40: 168-171, 2011.
8. Ottaviano G, Doro D, Marioni G, Mirabella P, Marchese-Ragona R, Tognon S, Marino F and Staffieri A: Extranodal Rosai-Dorfman disease: Involvement of eye, nose and trachea. Acta Otolaryngol 126: 657-660, 2006.
9. Dalia S, Sagatys E, Sokol L, and Kubal T: Rosai-Dorfman Disease: Tumor Biology, Clinical Features, Pathology, and Treatment Cancer Control October 2014, Vol 21, N 4.
10. McClain KL, Natkunam Y and Sverdlow SH: Atypical cellular disorders. Hematology (Am Soc Hematol Educ Program) 2004: 283-296, 2004.
11. La Barge DV III, Salzman KL, Harnsberger HR, Ginsberg LE, Hamilton BE, Wiggins RH III and Hudgins PA: Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): Imaging manifestations in the head and neck. AJR Am J Roentgenol 191: W299-306, 2008.
12. Zaveri J, La Q, Yarmish G and Neuman J: More than just Langerhans cell histiocytosis: A radiologic review of histiocytic disorders. Radiographics 34: 2008-2024, 2014.
13. Yu QJ, Zhuang H, Xia Y, Talati E and Alavi A: Demonstration of increased FDG activity in Rosai-Dorfman disease on positron emission tomography. Clin Nucl Med 29: 209-210, 2004.
14. Mosheimer BA, Oppl B, Zandieh S, Fillitz M, Keil F, Klauschofer K, Weiss G and Zwerina J: Bone Involvement in Rosai-Dorfman Disease (RDD): A Case Report and Systematic Review. Am J Dermatopathol 39: 27-32, 2017.
15. Thawerani H, Sanchez RL, Rosai J and Dorfman RF: The cutaneous manifestations of sinus histiocytosis with massive lymphadenopathy. Arch Dermatol 114: 191-197, 1978.
16. Wang KH, Chen WY, Liu HD, Huang CC, Lee WR and Hu CH: Cutaneous Rosai-Dorfman disease: Clinicopathologic profiles spectrum and evolution of 21 lesions in six patients. Br J Dermatol 154: 277-286, 2006.
17. Cole S and Finlay J: 2-Chlorodeoxyadenosine for adults with multi-system Langerhans cell histiocytosis. Med Pediatr Oncol 33: 512, 1999.
18. Rubenstein MA, Farnsworth WN, Pielop JA, Orenjo IF, Curry JL, Drucker CR and Hsu S: Cutaneous Rosai-Dorfman disease. Dermatol Online J 12: 8, 2006.
19. Hervier B, Harosche J, Arnaud L, Charlotte F, Donadieu J, Néel A, Ferro-Fabietti F, Villabona-Guerra B, Hermine O, et al: French Histiocytoses Study Group: Association of both Langerhans cell histiocytosis and Erdheim-Chester disease linked to the BRAFV600E mutation. Blood 124: 1119-1126, 2014.
20. Weitzman S and Jaffe R: Uncommon histiocytic disorders: The non-Langerhans cell histiocytes. Pediatr Blood Cancer 45: 256-264, 2005.
21. Emile JF, Abla O, Fraitag S, Horne A, Haroche J, Donadieu J, Requena-Caballero L, Jordan MB, Abdel-Wahab O, Allen CE, et al: Histiocyte Society: Revised classification of histiocytic disorders and neoplasms of the macrophage-dendritic cell lineages. Blood 127: 2672-2681, 2016.
22. O’Malley DP, Duong A, Barry TS, Chen S, Hibbard MK, Ferry JA, Hasserjian RP, Thompson MA, Richardson MS, Jaffe R, et al: Co-occurrence of Langerhans cell histiocytosis and Rosai-Dorfman disease: Possible relationship of two histiocytic disorders in rare cases. Mod Pathol 25: 1616-1623, 2010.
23. Juskevicius R and Finley JL: Rosai-Dorfman disease of the parotid gland: Cytologic and histopathologic findings with immunohistochemical correlation. Arch Pathol Lab Med 125: 1348-1350, 2001.
24. Kong YY, Kong JC, Shi DR, Lu HF, Zhu XZ, Wang J and Chen ZW: Cutaneous rosai-dorfman disease: A clinical and histopathologic study of 25 cases in China. Am J Surg Pathol 31: 341-350, 2007.
25. Bonetti F, Chierici M, Menedes F, Searpa A, Pelicci PG, Amorosi E, Gimona MA, Donati L and Knowles DM II: Immunohistological analysis of Rosai-Dorfman histiocytosis. A disease of S-100 + CD1 histiocytes. Virchows Arch A Pathol Anat Histopathol 411: 129-135, 1987.
26. Ying M, Ahuja AT and Yuen HY: Grey-scale and power Doppler sonographic imaging of unusual cutaneous lymphohistiocytosis. Ultrasound Med Biol 30: 449-454, 2004.
27. Karunanithi S, Singh H, Sharma P, Naswa N and Kumar R: 18F-FDG PET/CT imaging features of Rosai-Dorfman disease: A rare cause of massive generalized lymphadenopathy. Clin Nucl Med 39: 268-269, 2014.
28. Tsang JS, Anthony MP, Wong MP and Wong CS: The use of FDG-PET/CT in extranodal Rosai-Dorfman disease of bone. Skeletal Radiol 41: 715-717, 2012.
29. Albano D, Bosio G and Bertagna F: 18F-FDG PET/CT follow-up of Rosai-Dorfman disease. Clin Nucl Med 40: e420-e422, 2015.
30. Ha H, Kim KH, Ahn YJ, Kim JH, Kim JE and Yoon S-S: A rare case of Rosai-Dorfman disease without lymphadenopathy. Korean J Intern Med 31: 802-804, 2016.

31. Shaikh F, Awan O. Mohiuddin S, Farooqui S, Khan SA and McCartney W. 18F-FDG PET/CT Imaging of Extranodal Rosai-Dorfman Disease with Hepatopancreatic Involvement - A Pictorial and Literature Review. Cureus 7: e392, 2015.

32. Liu B, Lee NJ, Servaes S and Zhuang H: Rosai-Dorfman disease mimics lymphoma on FDG PET/CT in a pediatric patient. Clin Nucl Med 39: 206-208, 2014.

33. Deshayes E, Le Berre JP, Jouanneau E, Vasiljevic A, Raverot G and Seve P: 18F-FDG PET/CT findings in a patient with isolated intracranial Rosai-Dorfman disease. Clin Nucl Med 38: e50-e52, 2013.

34. Le Guenno G, Galicier L, Uro-Coste E, Petitcolin V, Rieu V and Ruivard M: Successful treatment with azathioprine of relapsing Rosai-Dorfman disease of the central nervous system. J Neurosurg 117: 486-489, 2012.

35. Huang JY, Lu CC, Hsiao CH and Tzen KY: FDG PET/CT findings in purely cutaneous Rosai-Dorfman disease. Clin Nucl Med 36: e13-e15, 2011.

36. Madhunapantula SV, Gowda R, Inamdar GS and Robertson GP: In situ photoimmunotherapy: A new hope for cutaneous melanoma patients. Cancer Biol Ther 10: 1088-1090, 2010.

37. Adeleye AO, Amir G, Fraifeld S, Shoshan Y, Umansky F and Spektor S: Diagnosis and management of Rosai-Dorfman disease involving the central nervous system. Neurol Res 32: 572-578, 2010.

38. Li M, Shi L, Luo M, Chen J, Wang B, Zhang F, Keyal U, Bhatta AK, Chen WR and Wang X: Successful treatment of Rosai-Dorfman disease using in situ photoimmunotherapy. Indian J Dermatol Venereol Leprol 83: 332-336, 2017.

39. Lu LY, Ju WT, Cai M and Lu XF: Cutaneous Rosai-Dorfman disease recurrence in infraorbital region. J Craniomax Surg 23: e509-e510, 2012.

40. Dalia S, Sagatys E, Sokol L and Kubal T: Rosai-Dorfman disease: Tumor biology, clinical features, pathology, and treatment. Cancer Control 21: 322-327, 2014.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.