

¹⁸F-fluoro-2-deoxyglucose positron emission-computed tomography in a rare cutaneous form of Rosai-Dorfman disease: A case report

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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 aforescribed 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 aforescribed masses, and pathology reported RDD.

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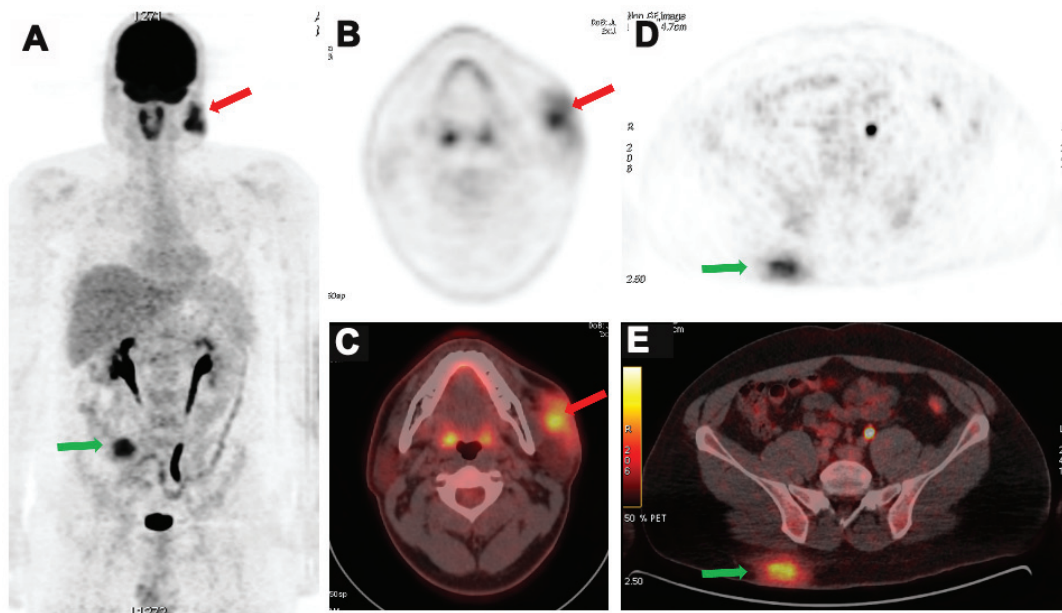


Figure 1. RDD diagnosis by ^{18}F FDG PET-CT. (A) Baseline whole body three-dimensional ^{18}F FDG PET-CT revealed the two hot spots of hypermetabolism located along the left cheek (red arrow) and the right gluteal region (green arrow), representing the subcutaneous masses of RDD. Axial cross-sections 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}F FDG PET-CT, ^{18}F -fluoro-2-deoxyglucose positron emission-computed tomography; PET, positron emission tomography; CT, computed tomography.

A total body ^{18}F 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 radiogluucose (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}F 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, 17 mm; SUV_{max} , 4.5) on follow-up ^{18}F FDG PET-CT imaging. Again, the RDD subcutaneous mass of the right gluteal region was excised surgically, with the initiation of steroid therapy, a first-line therapeutic option (9). Following the completion of steroid therapy after 24 months,

the ^{18}F FDG PET-CT follow-up performed at 24 months demonstrated a second recurrence of the right gluteal mass with an increase in size and metabolic activity of the single right paratracheal 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 Thawarani *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

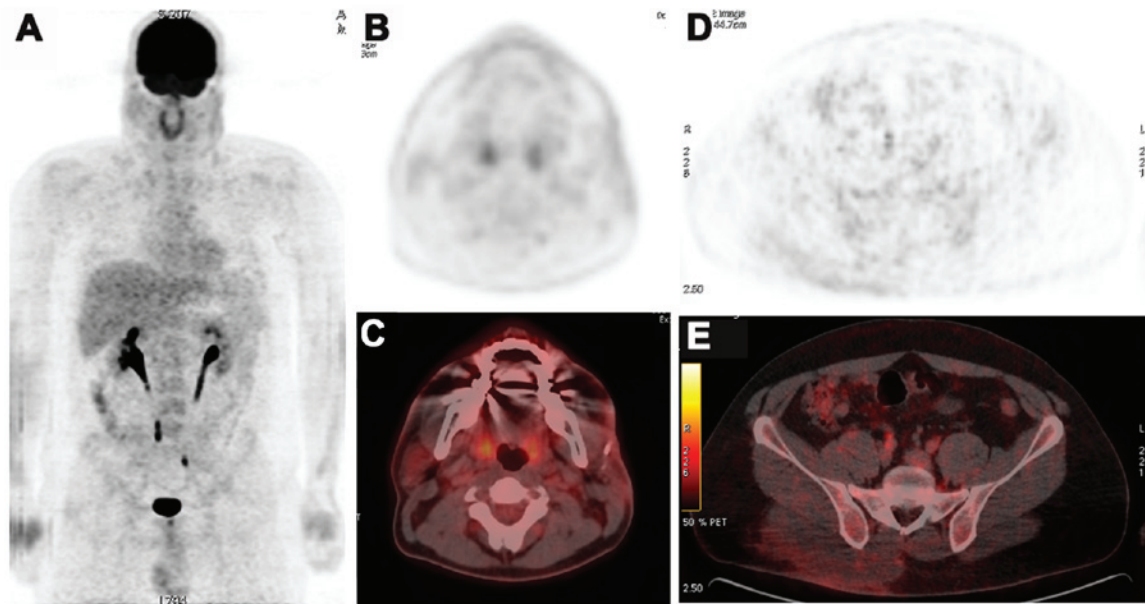


Figure 2. Follow-up ^{18}F FDG PET-CT after 8 months. (A) Whole body three-dimensional ^{18}F FDG PET-CT realized 8 months after surgical resection of the Rosai-Dorfman disease subcutaneous masses of the left cheek and the right gluteal region, with disappearance of the hypermetabolic hot spots previously observed on the baseline study. Axial cross-sections of (B) PET and (C) fused PET-CT of the head/neck. Axial cross-sections of (D) PET and (E) fused PET-CT of the pelvis. PET and fused PET-CT images revealed subcutaneous tissue thickening without increased uptake, a pattern consistent with post-intervention changes. ^{18}F FDG PET-CT, ^{18}F -fluoro-2-deoxyglucose positron emission-computed tomography; PET, positron emission tomography; CT, computed tomography.

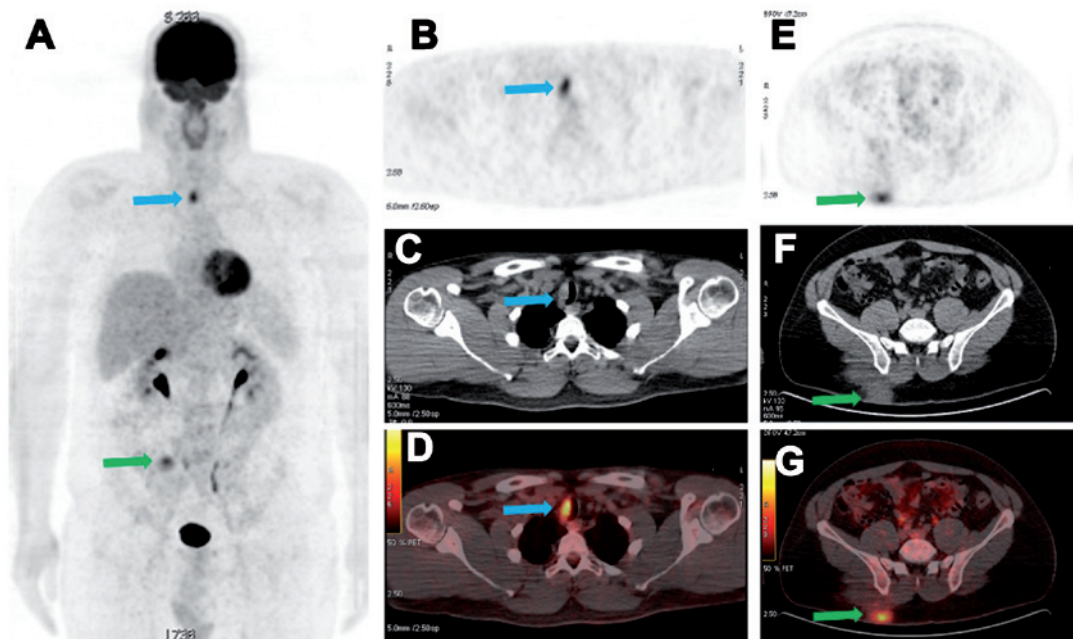


Figure 3. Follow-up ^{18}F FDG PET-CT after 24 months. (A) Whole body three-dimensional ^{18}F FDG PET-CT realized at 24 months. The patient had received a second surgical resection of the RDD subcutaneous mass of the right gluteal region within this time. Active foci were noted along the upper mediastinum (right paratracheal lymph node, blue arrow) and the right gluteal region (green arrow). The surgical bed of the left cheek was completely inactive following the initial and single surgical act. Axial cross-sections of (B) PET, (C) CT and (D) fused PET-CT of the thorax revealed the right upper paratracheal hypermetabolic lymph node (blue arrow). Axial cross-sections of (E) PET, (F) CT and (G) fused PET-CT of the pelvis revealed the subcutaneous hypermetabolic mass of RDD that relapsed following a second surgical excision (green arrow), instead of the initiation of steroid therapy. ^{18}F FDG PET-CT, ^{18}F -fluoro-2-deoxyglucose positron emission-computed tomography; PET, positron emission tomography; CT, computed tomography; RDD, Rosai-Dorfman disease.

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 histiocytes 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 emperipolesis 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 pale 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 emperipolesis 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 emperipolesis. 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 homogeneously 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 ^{18}F FDG-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 ^{18}F FDG PET-CT for monitoring steroid therapy, particularly in the visceral form of the disease (29,31). ^{18}F FDG 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 ^{18}F FDG PET-CT follow-up scans are available in literature. Notably, a case report of RDD mimicking a lymphoma on ^{18}F FDG 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 ^{18}F FDG-avidity was diagnosed as RDD of the central nervous system (CNS) (33). Follow-up on treatment responses using ^{18}F FDG 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 ^{18}F FDG 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 ^{18}F FDG 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. ^{18}F FDG 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 ^{18}F FDG PET-CT criteria. The elevated metabolic activity recorded in the present case of cutaneous lesions (SUV_{max} , 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 ^{18}F FDG 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-DG 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-DG PET-CT scan in English literature (35). Therefore, the present report described the second case of isolated cutaneous RDD evaluated by ¹⁸F-DG PET-CT scan, which displayed high radioglucose metabolism. The present case demonstrated the importance of ¹⁸F-DG PET-CT imaging in the screening of extranodal RDD, even with cutaneous involvement. In the latter case, ¹⁸F-DG 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.

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