



## Case report

# Localized retroperitoneal Rosai-Dorfman-Destombes disease as a cause of fever of unknown origin in adults. Case report and review of the literature



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## ABSTRACT

**Introduction:** Rosai-Dorfman-Destombes disease (RDD) is a rare “R” group histiocytic disease with a prevalence of 1:200,000. Herein, we present an extremely rare case with localized retroperitoneal RDD manifested as a fever of unknown origin (FUO). This case was managed in an academic setting and illustrates the challenging diagnostics of RDD and FUO.

**Presentation of case:** A 53-years-old female was admitted with complaints of night sweats, fever to 39.5 °C, 10 kg weight loss, fatigue, weakness, abdominal discomfort, and headache. On physical examination, there was no peripheral lymphadenomegaly or liver or spleen enlargement. Blood analysis revealed a hemoglobin 10.8 g/dL, elevated C-reactive protein level of 100.6 mg/L, and fibrinogen 6.57 g/L. Blood, throat, and urine cultures and serology tests were negative. Abdominal ultrasonography, transthoracic echocardiography, radiography, and computed tomography of the abdomen were normal. The PET scan showed a retroperitoneal conglomerate on the left side of the aorta. Subtotal resection of the conglomerate was performed. Microscopic examination revealed dilated sinusoids containing a large number of S100+ and CD68+ histiocytes, with marked emperipolesis. The patient recovered uneventfully. Eight months later, she was afebrile and free of complaints, with a 5 kg weight gain and negative PET/CT findings.

**Conclusion:** Localized abdominal RDD can cause FUO and should be considered in the differential diagnosis of localized retroperitoneal masses. PET/CT is useful for diagnosis, staging, and follow-up. Surgery is indicated for biopsy in cases of diagnostic uncertainty or decompression in symptomatic extranodal forms, but can be a definitive treatment for localized RDD.

## 1. Introduction

Rosai-Dorfman-Destombes disease (RDD) is a rare histiocytic disease first described by Destombes in 1965 and subsequently by Rosai and Dorfman as sinus histiocytosis with massive lymphadenopathy [1]. According to the revised classification of histiocytoses, it belongs to the “R” group with a prevalence of 1:200,000 [1,2]. It affects predominantly the lymph nodes, but in 43 % of the cases, there is extranodal involvement (skin, central nervous system, bones) [1,2]. RDD is typical for childhood and young adults but may occur at any age. The most common presenting symptom was painless bilateral cervical lymphadenopathy [3].

Herein, we present an extremely rare case with localized

retroperitoneal RDD manifested as a fever of unknown origin (FUO). FUO is defined as (a) febrile illness of >3 weeks' duration; (b) temperature >38.3 °C on at least 2 occasions; (c) without a diagnosis after a one-week hospital stay; (d) exclusion of immunocompromised persons (known HIV-infection, hypogammaglobulinemia, etc.) [4–6]. The patient was managed by the authors in an academic setting and illustrates the challenging diagnostics of RDD and FUO. This case report has been reported in line with the SCARE Criteria [7].

## 2. Presentation of case

A 53-years-old female was admitted with complaints of night sweats,

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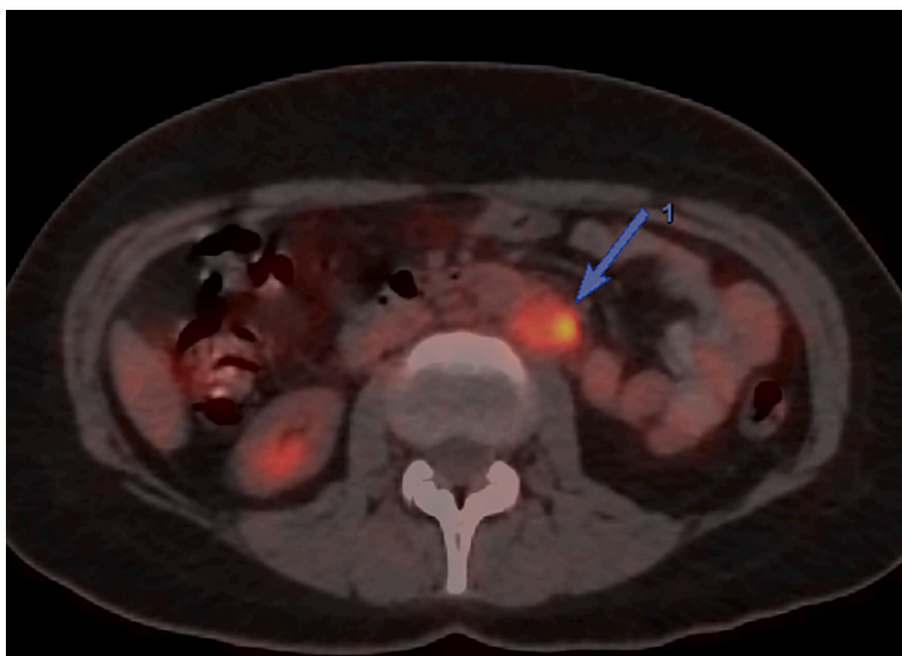
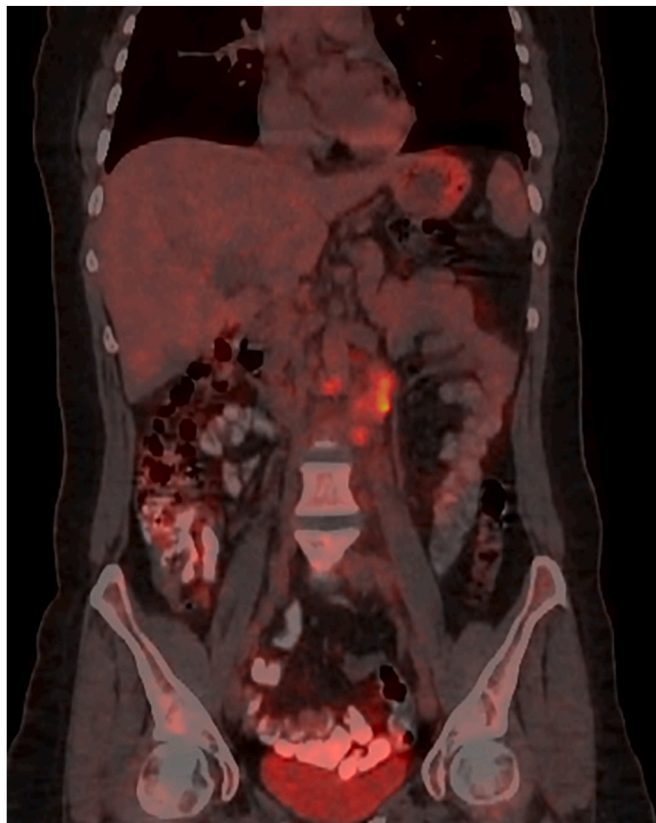
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fever to 39.5 °C, 10 kg weight loss, fatigue, weakness, abdominal discomfort, and headache. The patient's complaints started a month before admission. There was no relevant drug, family, surgical and psychosocial history. On physical examination, there was no peripheral lymphadenomegaly or liver or spleen enlargement. Blood analysis revealed only hemoglobin 10.8 g/dL, elevated C-reactive protein (100.6 mg/L and fibrinogen 6.57 g/L). Blood, throat, and urine cultures, and

serology for *Brucella* spp., *Chlamydia* spp., *Cytomegalovirus*, *Epstein-Barr virus*, *Francisella tularensis*, *HIV*, *Mycoplasma* spp., *Toxocara* spp., *Treponema pallidum*, and *Yersinia* spp. were negative. Serology for *Toxoplasma gondii* revealed false-positive results for IgM antibodies and negative results for IgG and IgA antibodies. Follow-up of IgM antibodies showed a trend toward normalization. AST-titer and RF factor were negative. Abdominal ultrasonography, transthoracic echocardiography,



**Figs. 1, 2.** PET/CT (192 MBq 18F-FDG, fixation time 80 min) revealed a localized retroperitoneal mass with increased uptake of FDG left to the aorta and single increased aortocaval lymph nodes.

radiography, and computed tomography (CT) of the abdomen were also normal. Consultation with a rheumatologist, cardiologist, or hematologist did not reveal any pathological findings.

This case was defined as FUO. Positron-emission tomography (PET) was performed according to the institutional algorithm [8]. It revealed multiple enlarged retroperitoneal lymph nodes with SUV 7.4. They were located between the inferior vena cava and left of the aorta from the bifurcation to the left renal vein (Figs. 1, 2). A perinodal infiltration of the adjacent soft tissues and thickened retroperitoneal fascia were also observed.

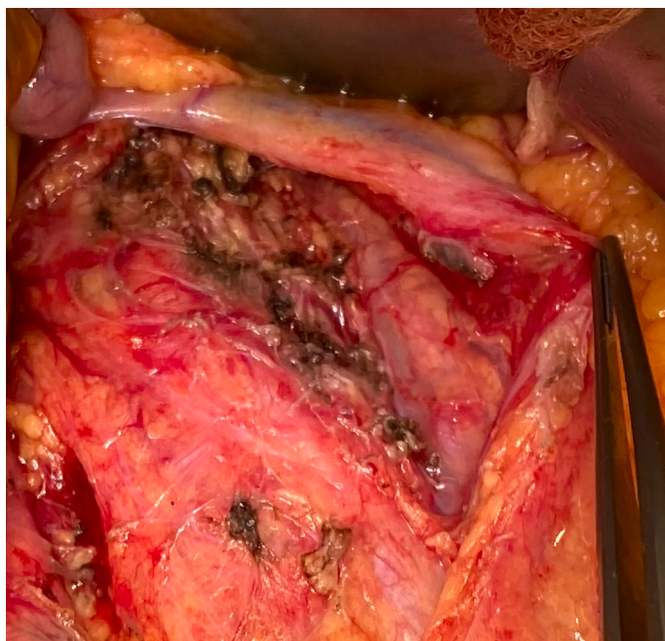
Due to persistent diagnostic uncertainty and based on the PET findings, exploratory laparotomy and biopsy were performed. The operation was performed by a senior surgeon. Well-demarcated enlarged lymph nodes between the inferior vena cava and aorta and a fibrotic conglomerate of lymph nodes located on the left side of the aorta and below the left renal vein were found. The aortocaval lymph nodes were removed completely, together with subtotal resection of the conglomerate (Fig. 3). There was no deviation from the initial management plan.

The microscopic examination revealed lymph nodes with marked fibrosis and dilated sinusoids containing a large number of S100+ and CD68 histiocytes with emperipolesis (Figs. 4 and 5). The cortex was dominated by CD5+ lymphocytes grouped into nodules. Abundant infiltration with CD 3, 10, 20, 23, Bcl2 and Cyclin D1 positive small lymphocytes was observed within the nodes and adjacent soft tissue.

The patient recovered uneventfully and was discharged on the fifth postoperative day. Eight months later, she was afebrile, free of complaints, and “extremely satisfied and happy”. Follow-up PET/CT results were negative (Figs. 6, 7).

### 3. Discussion

RDD belongs to the so-called “R group” histiocytosis. It is subdivided into four types: classic nodal (with or without IgG4 syndrome), extranodal (bone, spine, CNS, skin, kidney, single organ, or disseminated), neoplasia-related (leukemia, lymphoma, malignant histiocytosis associated), and autoimmune-related (systemic lupus erythematosus, juvenile idiopathic arthritis, autoimmune hemolytic anemia, etc.). It can be sporadic or familial [2]. Cutaneous RDD is a distinct entity that is a part



**Fig. 3.** Intraoperative view after the removal of the aortocaval lymph nodes (left) and subtotal removal of the retroperitoneal mass left to the aorta (right).

of the “C group,” histiocytosis. The extranodal form was observed in 43 % of the cases, with involvement of the CNS in <5 %, head, and neck in 11 %, intrathoracic in 2 %, gastrointestinal manifestation in 1 %, bones in 5–10 %, kidney in 4 %, and multisystem involvement in 19 % [1]. The etiology is still poorly understood and is beyond the scope of this study. RDD appears to be a polyclonal nonneoplastic disease with the most common mutations in KRAS, MAPK2K1, NRAS, and BRAF [1].

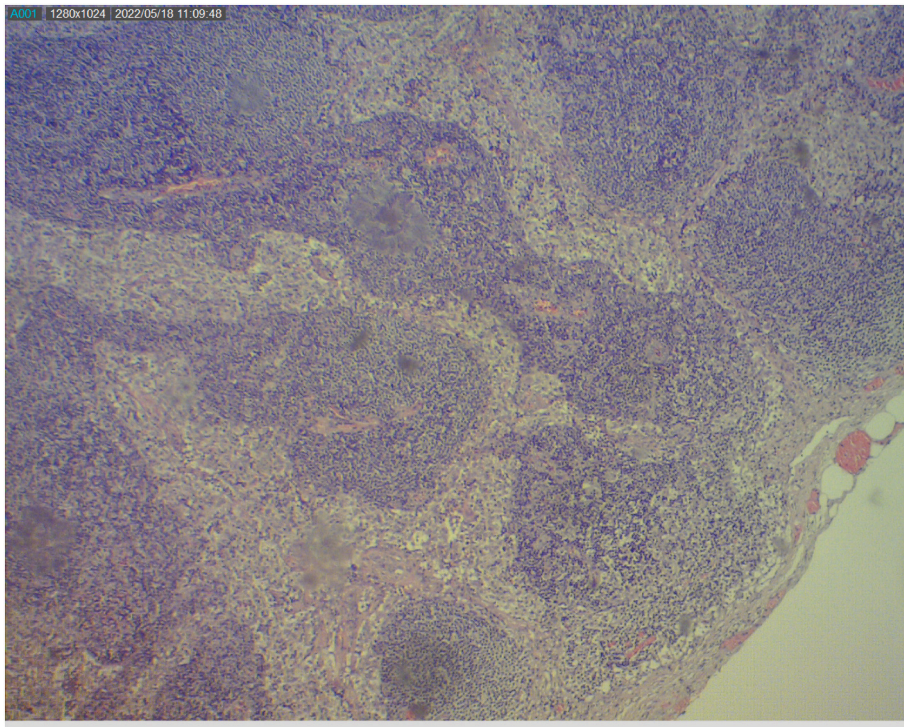
The most common clinical presentations of the classic nodal form are fever, bilateral cervical lymphadenopathy, fatigue, night sweats, and weight loss [1,3]. However, some series reported fever in only 38 % of the cases [9]. It can manifest as pronounced or mild abdominal pain, as in the present case. Normocytic normochromic anemia is typical with leukocytosis (neutrophilia) and thrombocytopenia [1]. Mediastinal, axillary, and inguinal lymphadenopathies may be present, whereas retroperitoneal lymphadenopathy is extremely rare.

The literature search in Pubmed using the keywords “isolated,” “retroperitoneal,” “nodal,” and “Rosai-Dorfman-Destombes disease” found a total of 13 papers since 1965. Only four patients reported retroperitoneal RDD [9–12]. Two reported retroperitoneal RDD, but none of them were localized, as in our case [9,12]. Sodhi et al. reported cervical and diffuse retroperitoneal RDD with compression of the aorta, inferior vena cava, and ureteric obstruction [10]. Gassel et al. published another case of retroperitoneal RDD with ureteral stenosis manifesting as exophthalmos due to a large mass in the left orbit and involvement of the paranasal sinuses (extranodal RDD) [11]. Moore et al. reported a 33-years-old female with RDD and synchronous aggressive diffuse large B-cell lymphoma, both diagnosed at autopsy [11]. At the onset, he had been operated on for a craniocervical tumor diagnosed as meningioma in Bulgaria and then re-operated in Germany, but the diagnosis of RDD had not been proven (histological diagnosis had been “inflammatory pseudotumor”). Eleven years later, he presented with exophthalmos and an orbital tumor. Tumor biopsy confirmed RDD. This case is illustrative of the diagnostic difficulties and can be considered the second case in our country. A short review mentioned a case of retroperitoneal RDD [9].

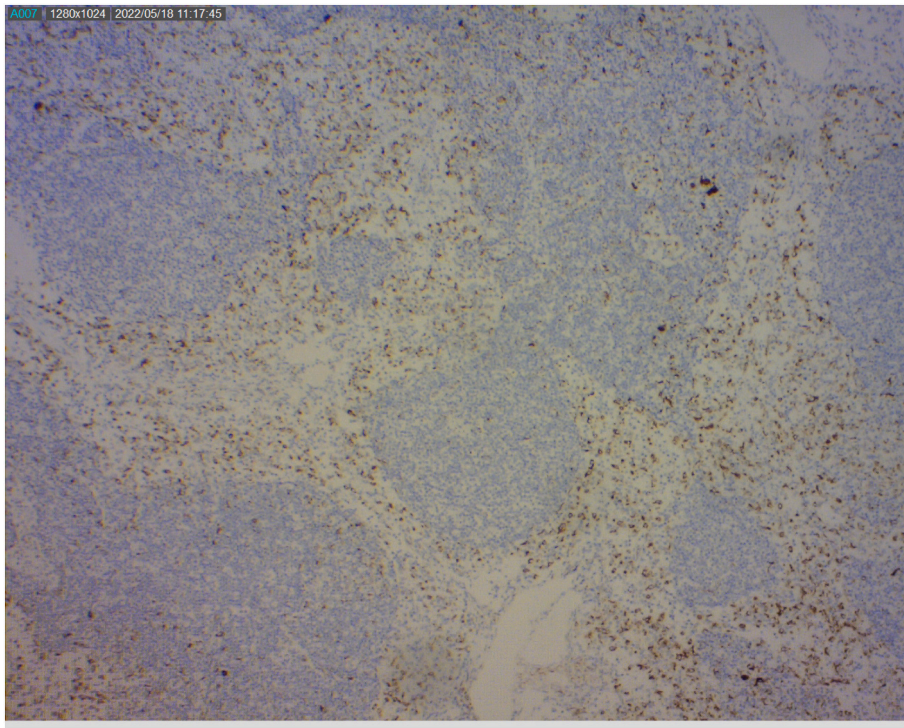
Preoperative diagnosis is challenging because of the need for a broad differential diagnosis. For example, 94 % of spinal RDD cases were preoperatively misdiagnosed [13]. In certain cases, it is impossible, as in the present case [11,12]. The organ-related symptoms require a specific differential diagnosis, which is given in detail in the Consensus recommendations from 2018 [1]. The main diagnostic pillars were medical history, physical examination, laboratory examination, and radiology. The classic clinical manifestations require differentiation from leukemia/lymphoma and autoimmune and infectious diseases.

According to our algorithm, in the case of FUO, the first step is a complete blood count, serum autoimmune/rheumatologic markers, and a panel for specific infectious diseases (*Brucella* spp., *Chlamydia* spp., *Cytomegalovirus*, *Epstein-Barr virus*, *Francisella tularensis*, *HIV*, *Mycoplasma* spp., *Toxocara* spp., *Treponema pallidum*, and *Yersinia* spp.), thyroid-stimulating hormone, interferon-gamma release assays, cryoglobulins, and direct microscopy of sputum [8]. In the absence of specific organ-related symptoms, PET/CT was indicated for the initial examination, as in the present case. The lymph nodes were hypermetabolic with increased FDG uptake, although this finding was not specific to RDD [14,15]. PET/CT is also an excellent tool for follow-up, especially in multiple RDD.

Grossly, the lymph nodes in RDD form a firm conglomerate with a yellowish appearance. Specific microscopic features include extensive sinusoidal expansion of S100+ histiocytes and abundant activated B cells, forming alternating dark and light areas [16]. Emperipolesis is another specific feature; histiocytes contain a large number of plasma cells and activated B-cell. The histiocytes were also positive for fascin, CD68, CD14, and CD163, but in contrast to Langerhans cell histiocytosis, they were CD1a- and CD207-negative. Differential diagnoses include sinus histiocytosis, Hodgkin lymphoma, Gaucher disease, Whipple disease, metastatic cancer, and malignant melanoma. The presence of RDD



**Fig. 4.** A histological view (hematoxylin Eosin, 4 $\times$ ) – lymph follicles with dilated sinusoids filled with histiocytes.



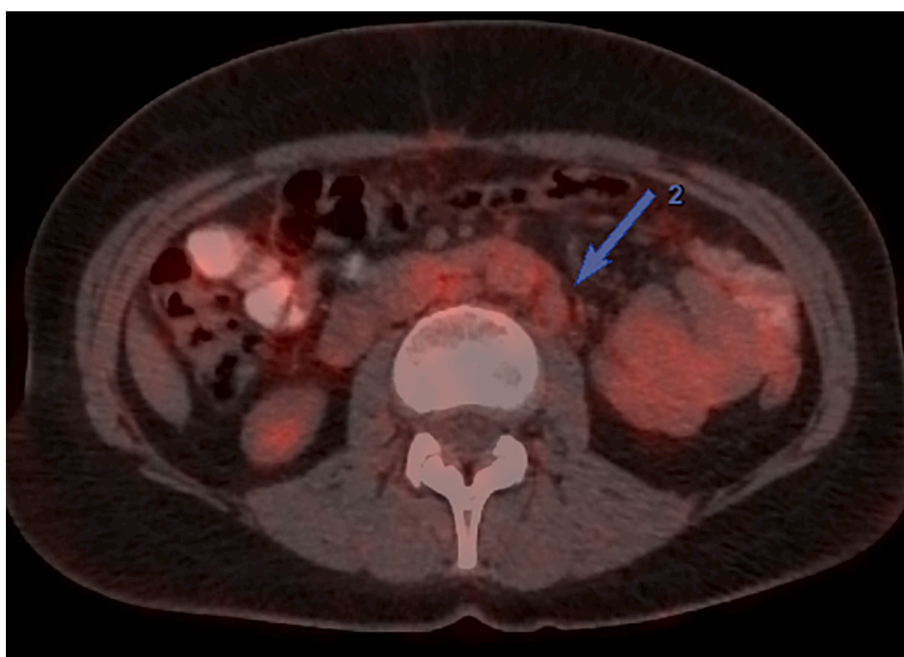
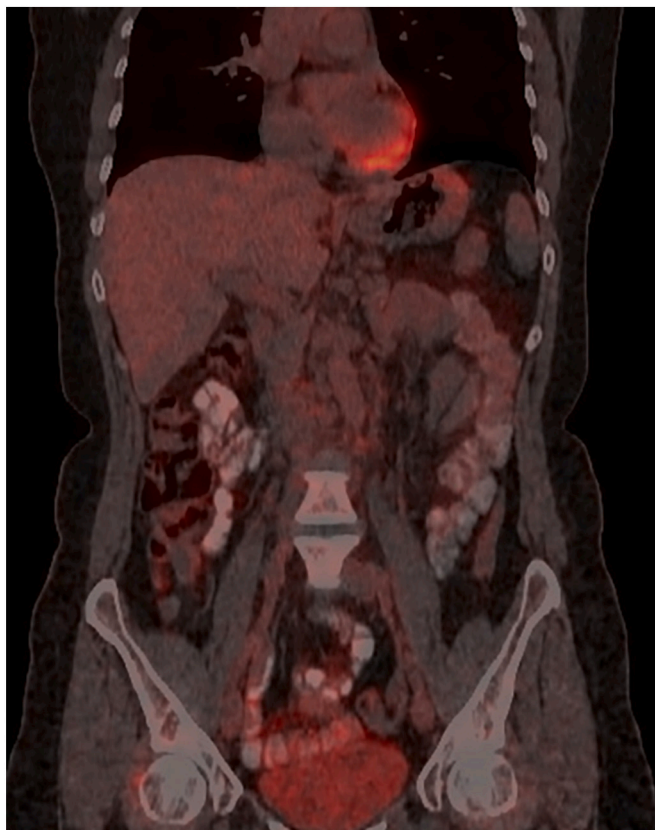
**Fig. 5.** CD68-positive histiocytes within the sinusoids.

characteristics in >10 % of the specimen in the case of coexisting pathology is associated with neoplasia-related RDD [16].

There is no consensus on the treatment of RDD [1]. As of today, there is no solid scientific evidence supporting a particular type of treatment. Most of these are empirical, experimental, and based on case reports and small series. Corticosteroids are appropriate for the initial treatment to

reduce the lesion's size and symptoms, but the response is variable with unpredictable duration. However, chemotherapy and immunomodulatory drugs have shown conflicting results. Radiotherapy can be used as a palliative treatment.

Surgery is indicated as biopsy in cases of diagnostic uncertainty, as in our case, or for decompression in symptomatic extranodal forms [17]. in



Figs. 6, 7. Follow-up PET/CT 8 months after the operation showed complete remission.

localized disease, it could be a definitive treatment. In the series of Pulsoni et al., surgery was effective in 89 % of cases [17].

Fortunately, RDD has a benign self-limiting course, with spontaneous regression in 50–83 % [1,16]. A lethal outcome may occur in 7–14 % due to infection and amyloidosis [17,18]. Renal involvement is associated with a 40 % mortality rate [1].

#### 4. Conclusion

Despite the casuist, localized abdominal RDD should be considered as a possible cause of FUO. It should be part of the broad differential diagnosis in cases of localized retroperitoneal masses. PET/CT is a useful tool for initial diagnosis, staging, and follow-up. Surgery is indicated for biopsy in cases of diagnostic uncertainty or decompression in symptomatic extranodal forms but can be a definitive treatment for localized

RDD.

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N/a.

#### Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

#### Author contribution

GP, VM, MB, PB, DP – study design, writing the paper, critical revision

MK – data collection, data interpretation, critical revision.

#### Research registration

N/a.

#### Guarantor

Georgi Popivanov.

#### Declaration of competing interest

The authors do not have a conflict of interest.

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