

CUTANEOUS ROSAI-DORFMAN DISEASE – A CLINICAL CASE

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Abstract

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Introduction. Rosai-Dorfman disease is a benign condition, characterized by self limiting proliferation of non-Langerhans histiocytes inside lymph nodes but also in extranodal areas.

Clinical case. A 54-year-old patient, diagnosed with arterial hypertension since 2011, is hospitalised in the Dermatology Department of the Emergency County Hospital, Craiova, Romania, in March 2016, for a polymorphous rash composed of violet-erythematous papulonodules with sizes ranging between 0.2 cm and 2 cm, slightly itchy, located in the latero-thoracic region, lumbar region and in the area around the menton area. The lesions appeared 18 months prior to hospitalization. Clinical and paraclinical investigations as well as interdisciplinary consultations revealed no associated pathologies. Histopathological and immunohistochemical examinations confirmed the diagnostic of cutaneous Rosai-Dorfman disease, imaging investigations excluding other localizations. Treatment with Doxycycline, in combination with 20 mg of Rutoside and 50 mg of ascorbic acid, Pentoxifylline and Levocetirizine resulted in remission of the skin lesions.

Discussion. Rosai-Dorfman disease is a rare condition, having a reported incidence rate of 1:200.000. It generally affects males, being more frequent in young males and people of African descent. The pathogenesis of Rosai-Dorfman disease is still not fully understood, although immunological and infectious factors may play an important role. Foucar has divided this condition into three types: nodal, extranodal and mixed. Cutaneous lesions have been described in 3% of cases of Rosai-Dorfman disease of the extranodal type. It is more frequent in females (sex ratio of 2/1) and in adults of Asian descent, with a mean age at onset of 45 years. Treatment options include: oral and intralesional corticosteroids, alfa-interferon, retinoids, dapsons, methotrexate, thalidomide, cryo- and radiotherapy.

Conclusions. The presented case is an atypical one because of the three locations of the skin lesions. Although we obtained remission of the disease, the patient would remain in direct observation because of the risk of recurrence.

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Introduction

Rosai-Dorfman disease (RD) is a benign condition of unknown etiology (1), characterized by self-limiting proliferation of non-Langerhansian histiocytes inside lymph nodes but also in extranodal areas (1, 2).

Clinical Case

A 54-year-old patient from a rural region is hospitalized in our Dermatology Department for a polymorphous rash composed of violet-erythematous papulonodules with sizes ranging between 0.2 cm and 2 cm, slightly itchy, located in the latero-thoracic region, lumbar region and in the area around the menton area. No family history to mention.

Personal pathological history: arterial hypertension since 2011, dyslipidemia since 2011, operated varicocele in 1984, appendectomy in 1993.

At home treatment: Indapamide 1.5 mg/day, Nebivolol 2.5 mg/day, Atorvastatine 20 mg/day, and Lercanidipine chloride 20 mg/day.

Disease history. The patient was hospitalised in the Dermatology Department of Craiova Hospital in March 2016, when he reported that the symptomatology appeared 18 months prior to hospitalisation. Initially, the lesions were localized in the menton area, later developed in the right latero-thoracic level (Figure 1) and left lumbar region (Figure 2). Outpatient treatment was composed of general treatment with hydrocortisone hemisuccinate, loratadine and diclofenac, and locally with fusidic acid and hydrocortisone, alternating with methylprednisolone acetate cream, with no favorable evolution.



Figure 1. Violet-erythematous papulonodules, 0.2-2 cm in diameter, slightly pruritic – right latero-thoracic



Figure 2. Papulo-nodules in the lumbar area

Patient examination: medium general state, overweight, type 3 phototype, nocturnal paresthesias of the hands, pain in the lumbar spine region and right knee, nycturia and slowed bowel movements.

Paraclinical investigations. Laboratory investigations (CBC, biochemistry, ESR) were all within normal limits, except for a 4% eosinophilia and dyslipidemia (high level of triglycerides: 245 mg/dL), and the serology for Hepatitis B and C were both negative. Serology for HIV and Treponemic infection were negative too.

Histopathological examination (Hematoxylin-Eosin staining) showed lymphoid structures in the dermal region, composed of histiocytes, lymphocytes, plasma cells, with nodular or insular disposition, which filled the dermis completely, some reaching even the hypodermis. The cells had large nucleus, round or oval in shape, vesicular and with an abundant eosinophilic cytoplasm (Figure 3 and 4). Emperipolesis was found (Figure 5): histiocytes that ingest inflammatory cells, a characteristic phenomenon of cutaneous Rosai-Dorfman disease, which can support the diagnosis.

Imunohistochemical tests revealed:

1. CD20 positive in follicular B structures, with a reactive immunohistochemical characteristic (KI 67 index high in germinative centers);
2. CD 5 positive in frequent paracortical type T small reactive lymphocytes;
3. Reduced KI 67 index (<5%);
4. CD 30 positive in isolated small lymphocytes;
5. Plasma cells with polyclonal characteristic – a kappa/lambda rapport of 1/1;

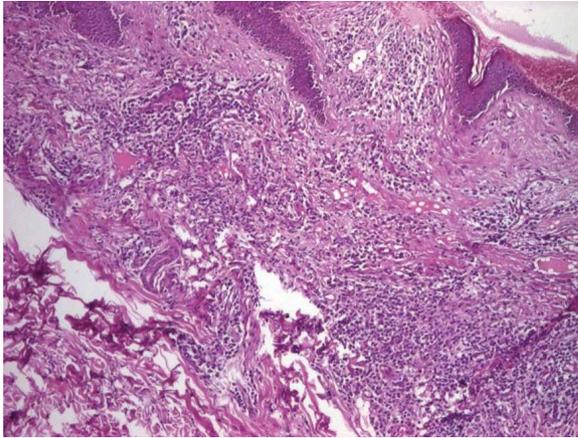


Figure 3. In the dermal region, lymphoid structures, composed of histiocytes, lymphocytes, plasma cells, with nodular or insular disposition, which filled the derma completely, some reaching even the hypodermis, Hematoxylin-Eosin staining, x40

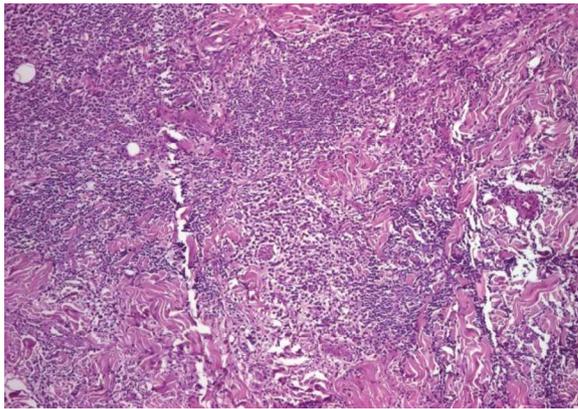


Figure 4. In the dermal region, lymphoid structures, composed of histiocytes, lymphocytes, plasma cells, with nodular or insular disposition, which filled the derma completely, some reaching even the hypodermis, Hematoxylin-Eosin staining, x40

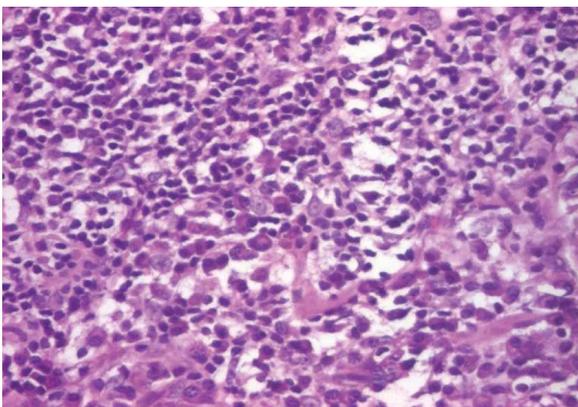


Figure 5. Emporipolesis phenomena: histiocytes who ingest inflammatory cells, Hematoxylin-Eosin staining, x400

6. S100 protein positive in frequent histiocytes, some with emperipolesis.

Chest X-ray did not show any active pleura-pulmonary processes, the heart was within normal limits, aorta with higher opacity. No images of possible secondary determinations were captured.

Abdominal and pelvic ultrasound: liver with a left lobe antero-posterior diameter of 7.7 cm, and a right lobe diameter of 13.5 cm, normal echogenicity, homogenous, without localized processes; gall bladder with thin walls, no stones; portal vein and primary biliary route of normal diameter; right kidney 11 cm in long axis, 4 cm transverse, parenchyma index of 15 mm, no stones, no dilations, vascularisation present; homogenous spleen, long axis of 10 cm; left kidney similar with the right kidney; hyperechogenous pancreas, relatively homogenous, normal sized; the bladder was empty, hard to visualize, with no liquid in the peritoneal cavity.

CT scan of the chest and abdomen: liver with a 1.8 cm image in the 7th segment subcapsular, spontaneous hypodens, well defined, with vascular capture in arterial phase and a tendency towards homogenization, which could be the expression of a capillary hemangioma; spleen 9/4.9 cm, with no retroperitoneal lymphadenopathies and no fluid in the abdominal cavity.

After *ophthalmological and neurological exams*, other localizations of the disease had been excluded. *Hematological examination* did not find any pathology.

Corroborating medical history with clinical manifestations and paraclinical investigations, we established the diagnosis of cutaneous Rosai-Dorfman disease.



Figure 6. Remission of skin lesions



Figure 7. Remission of skin lesions

Treatment was based on Doxycycline 100 mg, first two capsules a day for a month and then 100 mg/day for three months, and a combination of Rutoside 20 mg and ascorbic acid 50 mg (three capsules a day), Pentoxifylline 400 mg twice a day and Levocetirizin 5 mg/day. The patient's evolution was slightly favorable and therefore he was discharged.

After three months from discharge, the patient was readmitted to our Dermatology Department for reevaluation and extrainvestigations. Patient examination revealed disappearance of the lesions in the thoracic area (Figures 6 and 7). Laboratory analysis and inflammatory markers were within normal limits.

Discussion

Rosai-Dorfman disease was first described by Destombers in 1965 (1), and a year later by Azoury and Reed. In 1969, Juan Rosai and Ronald Dorfman reported a histiocytic affliction developed on a young black male, who presented with a massive cervical lymphadenopathy, bilateral, with no pain, associated with fever, anemia, neutrophilia, a high ESR and polyclonal gamopathy. The above-mentioned authors called this entity Sinusal Histiocytosis with Massive Lymphadenopathy (SHML). Given that lymphadenopathy does not appear in extranodal localizations, the term of SHML becomes incorrect, which is the reason why the eponym of Rosai-Dorfman is encouraged to be used (2).

Epidemiology

Rosai-Dorfman disease is a rare condition, with a prevalence reported at 1:200 000 people. It affects primarily males (58% males, 42% females), being

more frequent in young adults and people of African descent. In the literature, patients' age varied widely from one year old to 74 years old (3).

Approximately 13% of patients with Rosai-Dorfman disease associate immune afflictions such as uveitis, lupus erythematosus, rheumatoid arthritis, hypothyroidism and lymphomas (1). The most frequent association is with uveitis, which does not affect the disease prognostic, but increases morbidity (4).

The Pathogenesis of Rosai-Dorfman disease is not fully understood, although a disorder of the cell mediated immunity (5), immune factors and infections can play an important role (6). The polyclonal nature of the cellular infiltrate and the clinical progression of Rosai-Dorfman disease suggest rather a reactive process than a neoplastic one (7). In an article published in 1999, Middel *et al.* found that monocyte and macrophage stimulation by the macrophage colony stimulation factor (M-CSF) generated immunosuppressive macrophages. It appears that immunosuppressive macrophages represent the primary mechanism in the pathogenesis of Rosai-Dorfman disease (8). Six years later, Mannan *et al.* published a study in which they proposed that the dendritically cell would be the basis of origin of Rosai-Dorfman disease (9).

In some cases it was noticed that human herpes virus 6 (HHV 6) and Epstein-Barr virus (EBV) are associated with the pathogenesis (10). Luppi identified the expression of viral antigen of HHV 6 in two cases of Rosai-Dorfman disease (11). Also, Levine *et al.* published a study in which they used *in situ* hybridization to detect HHV 6 in patient tissue (10). Rarely, it can be associated with Brucella, Klebsiella rhinoscleromatis and Nocardia, although numerous studies could not confirm this association (1).

Histiocytosis represent a group of diseases characterized by histiocyte hyperproliferation. Histiocytes derive from the mononuclear phagocyte system, are capable to stock lipids and have a esterase, phosphates and lysozyme rich cytoplasm. They are antigens presenting cells towards lymphocytes, intervening in antibody and cellular mediated immune reactions, and ultrastructurally possess Birbeck granules (12, 13).

The World Health Organisation (WHO) classifies the lesion in a class II of histiocytosis syndromes, while The American Society for the Study of Histiocytosis places this entity in the group of macrophage conditions (2).

Foucar divided this disease in three subtypes: nodal, extranodal type and mixed (with organic and lymph node implication) (4). Extranodal types represent 43% of all cases of Rosai-Dorfman disease (15).

The superior respiratory tract is the most frequently affected, followed by the skin, eyes, retro-orbital tissue and bone tissue. Salivary glands and

Type	Syndrome
Dendritic cell	Langerhans cell histiocytosis
	Xanthogranuloma
Macrophages	Familial and reactive hemophagocytic lymphohistiocytosis
	Sinusal histiocytosis with lymphadenopathy (Rosai-Dorfman disease)
Malignant disorders	Monocytic leukemia
	Related to dendritic cells
	Located or related to macrophages
	Disseminated (malignant histiocytosis)

Table 1. Classification of histiocytosis (adapted after Favara BE, Feller AC, Pauli M, Jaffe ES, Weiss LM, Arico M, et al) (14)

central nervous system are less implicated. There have been reports of lung, uro-genital tract, gastro-intestinal tract, breast, thyroid and even heart affections (3).

Cutaneous Rosai-Dorfman disease was described for the first time by Thawerani *et al.* in 1978, when they reported the case of a 48-year-old patient who presented for a nodule in the capsular region and hypergammaglobulinemia (16). The cutaneous form is rare, representing 3% of all cases of extranodal type Rosai-Dorfman disease. Until the year 2008 there have been 80 reported cases. It is more frequent in females (sex ratio 2/1) and in adults with Asian descent, with a mean age of 45 years.

Kong *et al.* have described three types of cutaneous Rosai-Dorfman disease: papulo-nodular (79.5%), hardened plaques type (12.8%) and tumoral type (7.7%) (6).

Clinically, cutaneous Rosai-Dorfman disease is characterized by the presence of papule, nodules, plaques or tumors, light brown, dark brown or violet-red in color, with sizes ranging from 1 to 30 cm, localized or disseminated. The lesions most often appear in the head and neck region, in the thoracic region and later towards the extremities. The lesions could sometimes resemble acne or psoriasis (17).

Differential diagnosis: Langerhans cell histiocytosis, xanthogranuloma, reticulohistiocytoma cutis, skin lymphomas, Castleman disease (18, 12).

When cutaneous Rosai-Dorfman disease is suspected, it is important to exclude other histiocyte disturbances, especially *Langerhans cell histiocytosis*, which is a potentially lethal disease. Langerhans cell histiocytosis presents with cells with "coffee bean" nucleus; electronic microscopy can observe the Birbeck granules, and immunohistochemical tests are CD1a positive. The inflammatory infiltrate is rich in eosinophiles and lymphocytes, but with the absence of emperipolesis. It is

considered that any histiocytary lesion with rich eosinophiles infiltrate needs immunohistochemical studies to exclude histiocytosis with Langerhans cells (18).

Xanthogranulomatous conditions can present with a large variety of morphological characteristics, including vacuolated xanthomatous mononuclear cells with a tree-like appearance, pathognomonic for juvenile xanthogranuloma, or can present with neoplastic alteration in adult xanthogranuloma. Although giant multinuclear cells are present and help in classification of the conditions (giant Touton type cells in juvenile xanthogranuloma and giant Langerhans cells in adult xanthogranuloma) these are not pathognomonic. Giant multinucleated cells and also foamy histiocytes can also be observed in cutaneous Rosai-Dorfman disease. Thus, the presence or absence of emperipolesis is the most important histological characteristic which can help in distinguishing between the two diseases.

Also immunohistochemical studies can confirm the diagnosis, because xanthogranulomatous diseases are usually positive for factor XIIIa, CD68, CD163 and CD14, and negative for CD1a and protein s100 (18).

Differentiation between cutaneous Rosai-Dorfman disease and reticulohistiocytoma cutis is really difficult, because histiocytes from reticulohistiocytoma may present positive protein S100, but the ground-glass aspect of the histiocyte with rich cytoplasm, absent plasma cells and diffuse of emperipolesis may help to differentiate between the two entities (1).

Cases of malignant histiocyte conditions must also be excluded, including *Histiocyte sarcoma*, which is considered to be an extremely aggressive tumour. Foamy cells in the shape of a tree are present, though many of the histiocytes show a high grade of atypical shapes. Diagnosis is supported by the presence of CD68, which is accompanied any positive staining of lysozyme in 80% of cases.

Cases were reported of histiocyte sarcoma which began on the basis of a preexisting Rosai-Dorfman disease, although these cases were very rare. The characteristics of differentiation between the two entities are: cellular atypia, pleomorphism, invasion and destruction of tissues (18).

Treatment

Because cutaneous Rosai-Dorfman disease is characterized as a benign self limiting condition, with some cases in which spontaneous resolution is observed after months or years, therapy is recommended to be less aggressive. Surgical excision is recommended when the lesions are localized.

Cryotherapy, radiotherapy, topic or intralesional corticosteroids, dapsone (75 mg/day) and thalido-

mide (300 mg/day) have been reported to be efficient treatment (4, 19).

Favorable results have been obtained in some patients treated with Vinca alkaloids, tetracyclines and alchilation agents.

In a study by Pulsoni *et al.* in 2002, on a group of 12 patients, two of the subjects had favorable treatment response using 6-mercaptopurine and methothrexate (20).

Other systemic therapies used in Rosai-Dorfman disease are: imatinib, rituximab, 2-hlorodeoxiadenozine (2-CdA) and alfa interferon (19).

A case was reported of a 8-year-old boy presenting with a massive, painful lymphadenopathy that had begun three weeks prior, and was successfully treated with 2-chlorodeoxiadenozine, when conventional treatment (clarithromicine, doxycycline, augmentin and corticosteroids) had failed (20).

Jian-Xin Xia *et al.* have reported two cases, both of Asian descent, of cutaneous Rosai-Dorfman, respectively a 46-year-old woman, who presented with multiple papules and nodules on the left cheek that lasted for 10 years, and a second woman, aged 57, who presented with an itchy erythematous plaque that began seven months

earlier. Histopatological and immunohistochemical studies confirmed the diagnosis of cutaneous Rosai-Dorfman disease. The lesions improved after interlesional treatment with metamethazone and lidocaine, intramuscular interferon and oral acitretin, with no recurrence after an observation time of one year (21).

Conclusions

The case presented by us is atypical because of the triple localization of the lesions. Although we obtained remission of the disease, the patient would remain in direct observation because of the risk of recurrence.

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Conflicts of interest: none declared.

Patient consent obtained.

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