

## Rosai–Dorfman disease of vertebra: Case report and literature review

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Rosai–Dorfman disease is a rare benign histiocytic disorder that arises predominantly in lymph nodes with fever and malaise, but can affect various organs, with or without lymphadenopathy. Solitary extranodal skeletal lesions are extremely rare. Herein, we describe a case of isolated disease of thoracic spine, with vertebral body fracture.

A 14-year-old girl presented with cervical back pain for about one month as the only symptom. There was no lymphadenopathy. Results of laboratory tests were within reference ranges. The radiological examinations revealed collapse, osteolytic lesion and compressive fracture, which reduced vertical diameter of C4 vertebral body. The patient made a complete recovery after a limited C4 laminectomy, spondylodesis C3/C5 vertebra and biopsy of the lesion. Histologically, nonspecific cellular milieu and atypical histiocytic proliferation with emperipolesis, with CD68 and S100 positivity, confirmed a diagnosis of Rosai–Dorfman disease.

Isolated extranodal skeletal Rosai–Dorfman disease should be considered among the differential diagnoses of similar changes, such as Langerhans cell histiocytosis, Erdheim–Chester disease, eosinophilic granuloma, osteomyelitis, metastasis and lymphoma.

*Key words:* back pain, laminectomy, emperipolesis, sinus histiocytosis.

Rosai–Dorfman disease (RDD), also called sinus histiocytosis with massive lymphadenopathy (SHML) is a rare, sporadic disease which most commonly affects young adults and adolescents. The disease usually presents as painless, massive cervical and paratracheal lymphadenopathy in up to 90% of patients. Systemic symptoms are also common<sup>1-3</sup>.

Approximately 1100 patients have been reported with this disorder. About 45% of cases had at least one site of extranodal involvement as well as lymph node involvement, and about 20–25% of cases had extranodal involvement only. The most frequent extranodal sites are skin, soft tissue, nasal and orbital cavity, bone, salivary glands and central nervous system<sup>1-4</sup>.

Skeletal lesions are usually multifocal and mainly associated with lymphadenopathy and

disease in other organs<sup>4</sup>. A review of the literature reveals approximately 50 cases with solitary bone lesion as only manifestation of the disease<sup>4</sup>. To the authors' best knowledge; solitary lesions in the spinal column are described in 14 cases<sup>5-18</sup>. Vertebral body fracture is an extremely rare manifestation of RDD, which was previously reported in only one case<sup>17</sup>.

### Case Report

We presented a 14-year-old girl with intermittent cervical back pain and difficulties in mobility of the neck for about a month after gym exercises in school. There were no injuries of that part of the body or surrounding soft-tissue palpable mass. She had no other systemic symptoms such as fever, weight

loss, chills or malaise. We did not discover anything relevant from the past medical history. She did not have any surgical interventions before. There was no specific finding on physical and neurological examination. There was no lymphadenopathy. Results of routine hematologic and biochemical laboratory tests include erythrocyte sedimentation rate, C-reactive protein (CRP) and serum total proteins, albumin and immunoglobulins were within normal reference ranges.

A plain radiological examination of the cervical spine revealed physiological lordosis with collapse and osteolytic lesion of C4 vertebral body. The remaining bone structures were without significant changes (Figures 1a and 1b).

Preoperative computed tomography (CT) scan showed modified bone structure with osteolytic lesions of C4 vertebral body, which were extended to the right to processus transversus. Compressive fracture reduced the vertical diameter of the C4 vertebral body and made a deformation of the upper body surface in which the intervertebral disc C3/C4 was minimally impacted. There were also mild signs of anteriorly subluxation of C3 vertebral body.

Magnetic resonance (MR) image of cervical spine demonstrated reduced vertical diameter (4 mm) of C4 corpus due to complete spontaneous collapse of C4 vertebral body. In the posterior part of the collapsed vertebral body we identified the vertical fracture crack. The dislocated bone fragment in the dorsomedial direction was narrowing the spinal canal (8 mm) and compressed the spinal cord, but without myelopathy. Based on the intensity of MR signals we could not determine the cause of the collapse with certainty. Intervertebral disc C3–C4 and C4–C5 were intact. The remaining bone structures of the cervical spine and first five thoracic vertebral bodies were without significant changes.

CT of the chest, abdomen and pelvis was performed for preoperative evaluation and showed normal findings.

Corpectomy of C4 with decompression of the spinal canal from anterior side of C3 to C5 vertebral bodies was performed. The removed part of vertebra was sent for histopathologic analysis. Part of the left iliac crest was used for autotransplantation and reconstruction

as spondylodesis C3 to C5 vertebra was performed. She was discharged from hospital at postoperative 10 days without complications and additional medications, except some pain killers.

Histopathologic study of the lesion revealed atypical histiocytic proliferation with focal infiltration of medium to large histiocytes showing emperipolesis (Figures 2a and 2b). Nonspecific cellular milieu (lymphocytes, plasma cells, individual eosinophils and neutrophils) was also present. PAS and Zielh–Neelsen staining has not proved the existence of microorganisms. Immunohistochemistry stain showed that these histiocytes were positive for CD68, S-100, Lysozym and CD163, but negative for CD1a. In situ hybridization for EBV it had also showed negative.

Since then, the girl is in good general state with normal physical findings and laboratory analyses. However, after two years, upon one routine control we detected thrombocytopenia without manifested hemorrhagic syndrome. The investigations have verified that it was an immune thrombocytopenic purpura (ITP). On treatment with corticosteroids and i.v. immunoglobulins we achieved partial response. The disease has entered the chronic phase with signs of hemorrhagic syndrome. After a year, splenectomy, was performed but without improvement and after that the girl was treated with protocols of cytostatics and with rituximab, again with partial response. Now, she is in a stable phase of the disease (ITP), without therapy and also without any other complications related to the RDD and submitted to regular examinations by the hematologist in charge.

## Discussion

Sinus histiocytosis with massive lymphadenopathy or Rosai–Dorfman disease was first described by Destombes in 1965 and officially classified in 1969 by Rosai and Dorfman<sup>19</sup>. It is primarily a disease of childhood and early adulthood (mean age 20 years). No specific gender, ethnic, or socioeconomic predilection is encountered<sup>1,2</sup>. Considering its rare occurrence, approximately 1100 patients have been reported with this disorder, many are single case reports or descriptions of a small series of patients.



Fig. 1a and 1b. Radiological PA and profile findings of cervical spine showed collapse and osteolytic lesion of C4 vertebra body.

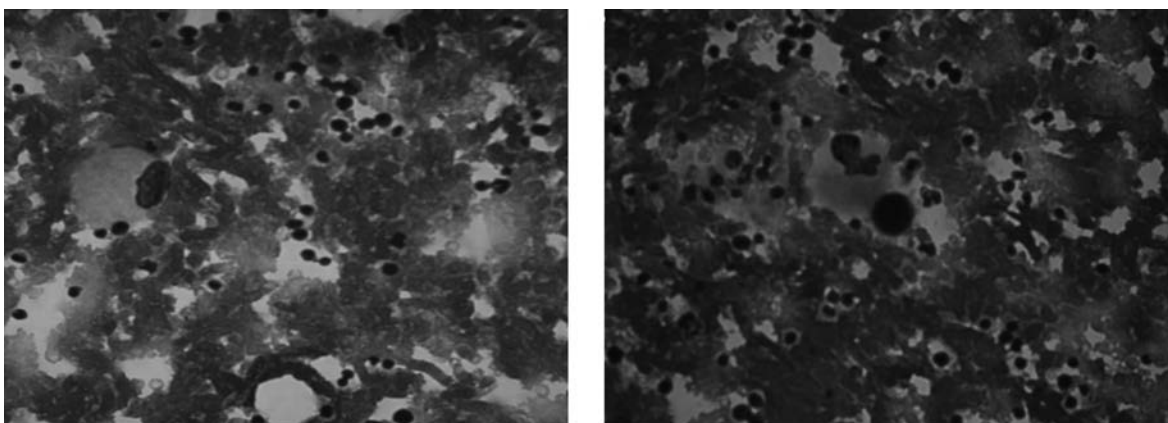


Fig. 2a and 2b. Nonspecific cellular milieu and histiocytic proliferation with the phenomenon of emperipolesis on the histopathologic preparation of bone biopsy sample.

RDD is characterized by an acquired, idiopathic, nonmalignant proliferation of distinctive histiocytes<sup>3</sup>. Painless, massive, bilateral, symmetric, cervical and paratracheal lymphadenopathy associated with the systemic symptoms (fevers, pain, tenderness, malaise, night sweats and weight loss) represents the most common clinical finding. Axillary, para-aortic, inguinal and mediastinal lymph nodes are also commonly affected. Bone marrow, liver and spleen are usually spared<sup>1-3</sup>. Besides affecting of the lymph nodes, about 45% of cases had at least one site of extranodal involvement. About 20–25% of cases had extranodal involvement only. The most frequent affecting extranodal sites are skin, soft tissue, nasal cavity and paranasal sinuses (16%); eye, orbit and bone (11%), salivary gland and central nervous system (7%) and significantly rarer oral cavity, kidney, respiratory tract, liver,

tonsil, breast, gastrointestinal tract and heart. Whether nodal and/or extranodal RDD is often under-diagnosed because of a low index of suspicion of this disease<sup>1-4</sup>.

Skeletal lesions are usually multifocal and such involvement is mainly associated with lymphadenopathy and disease in other organs<sup>4</sup>. Patients with the disease who present with a solitary lesion of bone but without additional clinical manifestations are exceedingly rare and the majority of these patients have been in adults<sup>4,20</sup>. A review of the literature reveals approximately 50 cases with solitary bone lesion as the only manifestation of the disease. Lesions arise most frequently in the long bones such as tibia, femur, radius, clavicle, also in the pelvic bones, skull bones, maxilla, mandible and bones of the hands<sup>4,20</sup>.

The present case is a rare example of compression fracture caused by isolated

**Table I.** Reported Cases of Extranodal Rosai–Dorfman Disease Localized in the Spinal Column Without Lymphadenopathy

Authors / year	Age	Sex*	Localization**	Symptoms	Treatment	Outcome
Chan et al./1985 <sup>5</sup>	7	F	C6 vertebral pedicle, C6–T1 epidural mass, cord compression)	quadriparesis, neck pain, torticollis, difficulty in urination, anorexia	laminectomy	stable
Hollowell et al./2000 <sup>6</sup>	71	M	C6– L2 (epidural mass, cord compression)	pain, parasthesis, weakness of legs	incomplete resection, steroids	significant neurologic improve
Hargett et al./2005 <sup>7</sup>	29	F	T5–T9 (epidural mass, cord compression)	progressive paraplegia, leg pain	pedicle screw fixation and fusion, radiation	stable
Tubbs et al./2005 <sup>8</sup>	13	M	craniocervical junction (epidural mass, cord compression) + mastoid and parietal bone	neck pain, palpable neck mass, sinusitis, mastoiditis	partial resection, steroids, antimetabolite therapy	stable
Al–Saad K et al./2005 <sup>9</sup>	17	M	T9 vertebral body, epidural mass T8–T10 (cord compression) + tibia	back pain, weakness of legs	steroids, laminectomy	stable
Robert et al./2006 <sup>10</sup>	23	F	Sacrum	/	/	/
Huang et al./2007 <sup>11</sup>	31	F	T6–T8 (epidural mass, cord compression)	paraparesis, back pain, difficulty in urination. relapsing uveitis	laminectomy	stable
Gupta et al./2008 <sup>12</sup>	16	M	T12 vertebral body	back pain, leg numbness, soft tissue mass	laminectomy	stable
Jing et al./2008 <sup>13</sup>	51	F	T11 vertebral body (cord compression)	/	Fine–needle biopsy	/
Abou–Zeid et al./2010 <sup>14</sup>	24	M	T4–T7 (epidural mass, cord compression) later T8/9	progressive spastic paraparesis	laminectomy, later subtotal resection with pedicle screw fixation	significant neurologic improve
Raslan et al./2011 <sup>15</sup>	57	F	T9 (vertebral body, cord compression) + maxillary sinus	back and chest pain	laminectomy, radiotherapy	stable
Parmar et al./2013 <sup>16</sup>	64	M	C6 vertebral body	pain, weakness of limbs, parasthesis	laminectomy	stable
Kim et al./2014 <sup>17</sup>	15	M	T12 vertebral body (fracture)	back pain	laminectomy	stable
Sciacca et al./2015 <sup>18</sup>	75	F	T10 vertebral body (cord compression)	Paraparesis, weakness of limbs, parasthesis	Steroids, hemi – laminectomy	stable

\*F – female, M – male \*\*C – cervical, T – thoracic, L – lumbar

extranodal RDD involving the cervical spine without lymphadenopathy and other symptoms. To the authors' best knowledge, solitary lesion in only one vertebral body or vertebral pedicle is described in ten cases<sup>5, 8-10, 12, 13, 15-18</sup>, of which in three cases with lesions in other parts (mastoid/parietal bone, tibia, maxillary sinus)<sup>8,9,15</sup>. In three of these cases solitary lesion in one vertebral body is associated with an epidural mass<sup>5,8,9</sup>. Solitary epidural lesion alongside several vertebral bodies is described in another four cases<sup>6,7,11,14</sup>. Vertebral body fracture is an extremely rare manifestation of RDD, which was previously reported in only one case<sup>17</sup>. Only 5 cases were described in childhood<sup>5,8,9,12,17</sup> and it is interesting that the same number was recorded in the age group over 50 years<sup>6,13,15,16,18</sup>. In Table I, we presented the comparison of all cases of isolated RDD localized in the spinal column. Also, there have been few cases described of intraspinal or intradural involvement, but they did not take into comparison.

Spinal involvement is mostly causing neurologic deficit due to spinal cord compression<sup>5-9, 11, 13-15, 18</sup>. Treatment is also individual. Prognosis of primary osseous RDD is good, although there is no consensus within the medical community for effective treatment. In most cases a neurosurgery intervention, was sufficient while in others it was necessary to administer systemic corticosteroids, radiation therapy and/or chemotherapy (vinca alkaloids or 6-mercaptopurine and oral methotrexate)<sup>1-3</sup>.

RDD shows a variety of imaging manifestations. These lesions are typically intramedullary osteolytic, with either poorly or sharply defined margins, rarely mixed lytic sclerotic or sclerotic. That can be confused radiographically with Langerhans cell histiocytosis (LCH), eosinophilic granuloma or other lymphocyte proliferative diseases. The differential diagnosis also includes bacterial osteomyelitis, fungal infections such as histoplasmosis, metastasis and lymphoma. Other conditions varying from benign to malignant such as giant cell tumor, granulomatous diseases, fibrous dysplasia and Ewing sarcoma/primitive neuroectodermal tumors (PNET) have also been described in the differential<sup>3, 21</sup>.

Juvenile Xanthogranuloma (JXG) and Erdheim-Chester disease (ECD) are, like RDD, types

of non-Langerhans histiocytosis and share some pathological and immunohistochemical features with RDD<sup>1</sup>. Clinically, JXG is a pediatric histiocytosis characterized mainly by xanthomatous skin lesions, but vertebral involvement is rarely seen. On the other hand, ECD is a rare manifestation in childhood and involves multiple organs, with symmetrical long bone involvement, but atypical vertebral involvement with neurological symptoms in children has been described in the literature<sup>22</sup>. These entities should also be taken into consideration in the differential diagnosis.

There is no specific serological marker for diagnosis. However, patients have an elevated erythrocyte sedimentation rate, leukocytosis with neutrophilia and hypergammaglobulinemia in up to 90%<sup>1-3</sup>. Our case during active disease had laboratory analysis in the normal range.

Diagnosis of extranodal skeletal RDD rests entirely on biopsies and pathohistological examinations. The most useful immunohistologic marker for SHML histiocytes is the expression of the S100 protein. SHML histiocytes express pan-macrophage antigens (CD68, HAM 56, CD14, CD64, CD15), antigens associated with phagocytosis (CD64), lysosomal activity (lysozyme, alpha-1-antitrypsin) and immune activation (transferring receptor, interleukin-2 receptor). Only rare CD1a positive cells are found in SHML<sup>1-3</sup>. Vertebral involvement and collapse of the vertebral body is a common condition in LCH. Considering that CD1a is a diagnostic marker for LCH, but at times may be false negative and very rarely negative; in unclear cases the determination of langerin (CD207) positivity is important for definitive diagnosis of LCH<sup>23</sup>. Langerin expression was not done in our case for technical reasons.

Some authors claim that RDD represents the immune deregulatory process. Autoimmune hemolytic anemia as the most frequent immune dysfunction, and polyarthralgia, rheumatoid arthritis, glomerulonephritis and diabetes mellitus are known to complicate SHML<sup>1-3</sup>. Immune thrombocytopenic purpura has not yet been described in the literature as a complication of RDD. However, we cannot claim with certainty that this autoimmune process is associated with the underlying disease and ITP should not be considered as

complication of RDD.

Extranodal skeletal solitary manifestation of RDD is an extremely rare condition, especially with involvement of the spine vertebra. Because of its rarity, various clinical manifestations and radiologic findings, it was difficult to differentiate from other common diseases on radiologic study alone, so pathologic confirmation was needed. If a young adult or adolescent has compression of the vertebra body, diagnosis of RDD can be considered.

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