Craniocervical Rosai-Dorfman Disease Involving the Vertebral Artery: Case Report and Literature Review

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Key words
- Craniocervical
- Foramen magnum
- Radiotherapy
- Rosai-Dorfman disease
- Surgical resection
- Vertebral artery

Abbreviations and Acronyms
CNS: Central nervous system
RDD: Rosai-Dorfman disease

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BACKGROUND: **Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a rare non–Langerhans cell reactive histiocytic disorder that rarely occurs in the central nervous system (CNS). Extranodal RDD most frequently involves the skin, upper respiratory tract, soft tissue, gastrointestinal tracts, bones, breast, and CNS.**

CASE DESCRIPTION: **RDD of the CNS infiltrates most commonly the dura of the sella, cavernous sinus, and the periclival regions. It is usually clinically and radiologically mistaken for meningioma because of its focal dural-based aspect. RDD is confirmed histologically by lymphoplasmacytic cells and histiocytes of varying size showing emperipolesis (lymphocytophagocytosis). To date, only 4 cases of RDD displaying spinal cord compression secondary to craniocervical junction involvement have been reported.**

CONCLUSION: **We report the case of a patient diagnosed with RDD localized at the foramen magnum extending to the base of the odontoid process and involving the V4 segment vertebral artery.**

INTRODUCTION

Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a rare histiocytic proliferative disorder of unknown cause that was first described as a distinct clinicopathologic entity in 1969.[1] Although the classical presentation of RDD is that of massive, bilateral, painless cervical lymphadenopathy, extranodal involvement at diverse sites can occur and usually presents with other constitutional symptoms such as fever, malaise, weight loss, and raised inflammatory markers.[2] Extranodal involvement can be found in 43% of cases sustained with RDD, and the primary extranodal sites include skin, orbit, upper respiratory tract, and bones.[3] Central nervous system involvement is particularly rare (<5% of extranodal RDD), and most cases occur intracranially.[4] So far, only 4 cases of RDD displaying spinal cord compression secondary to craniocervical junction involvement have been reported.[5-8] The present report illustrates a case of RDD localized at the foramen magnum extending to the base of the odontoid process and involving the vertebral artery.

CASE REPORT

History and Examination

We report the case of a 54-year-old man from Sudan with a history of myocardial infarction 2 years ago maintained on aspirin, who initially presented to the neurosurgery outpatient clinic for posterior neck pain of 6 months' duration. The pain was not related to movement and worsened progressively over time. The pain was described as radiating to the left and right shoulders, and was associated with bilateral hand numbness. A few months before presentation, the patient noticed mild weakness of the left arm and left leg. He also reported recent difficulty in swallowing and dysphonia. On neurologic examination, the patient demonstrated left upper extremity weakness (3 out of 5), lower extremity weakness (4 out of 5), and hyperreflexia in all limbs. Shoulder elevation was weak on the right and left sides. Hypoesthesia of the left fingers was noticed on examination. Magnetic resonance imaging of the brain with and without gadolinium revealed a well-circumscribed mass of 30 × 25 × 19 mm in the largest antero-posterior diameter, located in the foramen magnum and reaching the base of the odontoid process, left anterolateral to the spinal cord and medullary spinal junction surrounding the left vertebral artery. The mass showed local meningeal enhancement compatible with meningioma (Figure 1).

Operation

Written consent was obtained from the patient before the surgery. After putting the patient in a three-quarter position with the side of the tumor up, we did a retroauricular incision in an S shape reaching medially inferiorly to the spinous process of C2.

Under sterile conditions, we opened the skin incision and cut through the neck

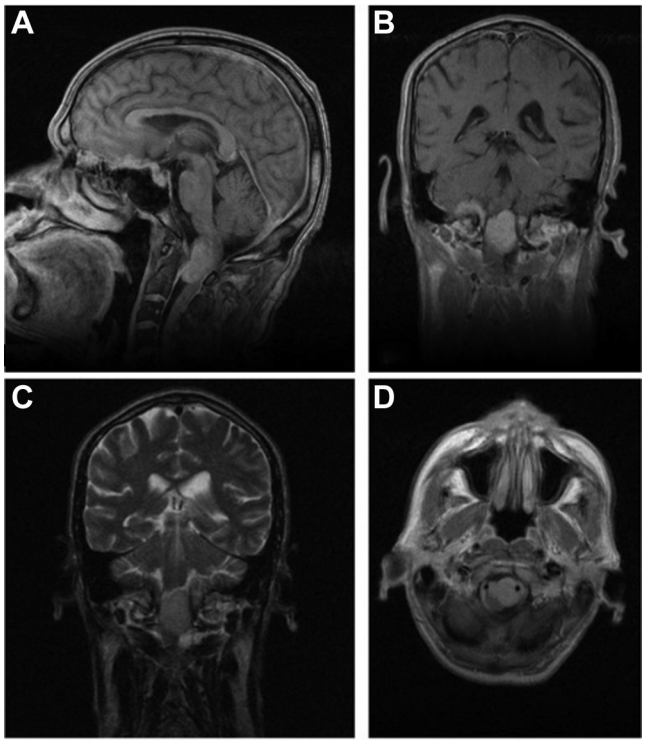

Figure 1. Preoperative magnetic resonance imaging with sagittal (**A**), coronal (**B** and **C**), and axial cuts (**D**) showing the extent of the tumor to the base of the odontoid and surrounding the left vertebral artery.

muscles reaching the suboccipital lateral area. Then we went medially to the ligamentum nuchae, which we opened to expose the posterior arch of C1 and the spinous process of C2. Because of this, we are oriented to the bony structures of C1 and C2. This is very important to prevent vertebral artery injury. Then subperiosteal dissection was started at the posterior arch of C1 inferiorly medial to lateral with the periosteal elevator until we identified the sulcus arteriosus, where the extradural part of the vertebral artery passes before it enters the dura. Once identified, we continued the dissection along the inferior edge of the C1 posterior arch until we reached the transverse process of C1. This is done in case vertebral artery mobilization is needed; in this case, we drilled the transverse process of C1. Because the patient had a dehiscent transverse process, we could see the vertebral artery through the bone in the transverse process. The vertebral artery with the surrounding venous plexus was followed carefully subperiosteally in the sulcus arteriosus in the C1 posterior arch until we reached the dural entry point. Care must be taken not to injure the posterior inferior cerebellar artery if it is coming extradurally and the muscular branch of the vertebral artery. At this stage, we found the occipital condyle just lateral to the vertebral artery before it entered the dura articulating with the lateral mass of C1. Then the patient underwent suboccipital lateral craniotomy or craniectomy. The dura and sigmoid sinus were exposed. Then we started drilling the condyle superiorly lateral to medial until we identified the condyle vein. This ended the cranial drilling; after that, we started drilling the posterior arch of C1 with the diamond drill starting from the transverse process of C1 to the near midline. This was done after releasing and mildly transposing the vertebral artery superiorly and laterally. Then under a microscope, we started opening the dura a few millimeters medial to the entry of the vertebral artery superiorly and inferiorly. At this stage, we could identify the tumor and the cord and the cerebellum with the lower cranial nerves. The tumor was debulked with a Cavitron Ultrasonic Surgical Aspirator (Integra Life Sciences, Dublin, Ireland) until we identified the vertebral artery and medially the basilar artery. The tumor surrounded the vertebral artery and was very stuck to it. Therefore, we opted to leave a few millimeters of tumor at the vertebra–basilar artery junction. We assumed near-total resection of the tumor as shown in Figure 2. Postoperatively, the patient improved tremendously and was discharged after 2 days.

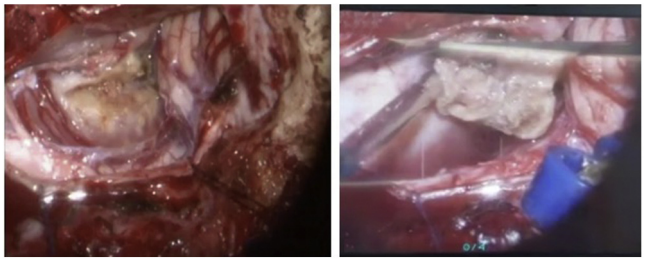

Figure 2. Intraoperative images showing the tumor location before and after resection.

Pathologic Findings

Histopathologic examination showed that the lesion was composed of sheets of foamy histiocytes, multinucleated giant cells, lymphocytes, and plasma cells. Numerous histiocytes showed emperipolesis. Granulomas and necrosis were not present. Grocott's methenamine silver stain and acid-fast bacilli histochemical stains were negative for microorganisms. The neoplastic histiocytes were positive

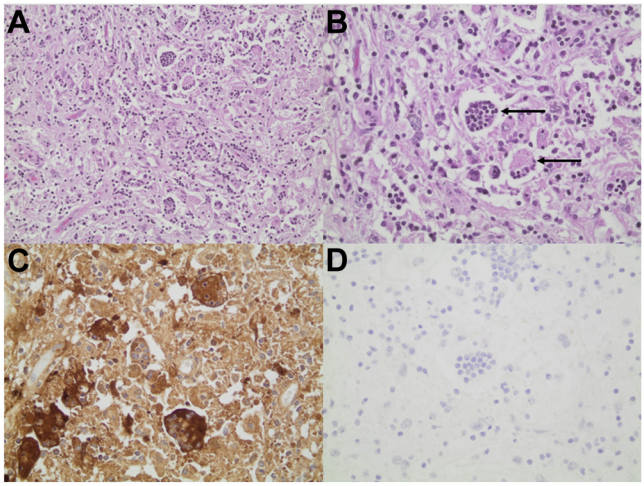

Figure 3. (**A**) The lesion is composed of sheets of histiocytes, lymphocytes, and plasma cells (hematoxylin and eosin [H&E] stain; original magnification, 200×). (**B**) Numerous histiocytes show emperipolesis (*arrows*) (H&E stain; original magnification, 400×). (**C**) S-100 is positive in Rosai-Dorfman histiocytes and highlights engulfed lymphocytes as negative images (S-100 immunostain; original magnification, 400×). (**D**) Cluster of differentiation 1a (CD1a) is negative (CD1a immunostain; original magnification, 400×).

for S100 and CD68 immunohistochemical stains. Contrary to Langerhan cell histiocytosis disease, the histiocytes were negative for CD1a. They were also negative for BRAF V600E mutation by immunohistochemistry (Ventana-VE1), unlike in some cases of Langerhan cell histiocytosis disease and Erdheim-Chester disease. The overall findings support a diagnosis of RDD (Figure 3).

Postoperative Course

The patient's motor weakness in the left upper and lower extremities improved after surgery, but he still complained of residual paresthesia in the left hand. The case was discussed at the multidisciplinary neuro-oncology tumor board. The patient was subsequently treated with 3-dimensional conformal radiation therapy, receiving a total dose of 20 Gy in 10 fractions. The patient's posttreatment radiation course was not complicated.

DISCUSSION

RDD is a histioproliferative disease of unknown origin that was first described in 1969.[1] Mostly cases occur during the third and fifth decade of life, but a few are reported in the pediatric population and older adults.[9] It usually presents with cervical lymphadenopathy, fever, leukocytosis, elevated erythrocyte sedimentation rate, and hypergammaglobulinemia.[2] Extranodal RDD occurs in 25% of cases and may arise in the orbit, nasopharynx, respiratory pathways, gastrointestinal tract, endocrine glands (particularly the thyroid), bone, skin, and central nervous system (CNS). Involvement of the CNS in RDD is rare (approximately 5%).[3] A review of the CNS manifestations of RDD reveals that most patients present with focal dural-based hemispheric brain lesions mimicking meningioma.[10] Definitive diagnosis of RDD is based on the neuropathologic hallmark of the disease which is characterized by diffuse histiocytosis and emperipolesis.[11] In most cases, RDD infiltrates the dura of the sella, cavernous sinus, and periclivial regions. Spinal RDD constitutes only 20% of reported CNS cases. So far, 4 cases of RDD causing compressive cervical myelopathy at the craniocervical junction have been reported (Table 1).[5-8] The presented case was quite atypical because of the involvement of the intradural left vertebral artery in the lesion extending from the foramen magnum to the base of the odontoid process. Consequently, the lesion was partially resected because of engulfment and adherence to the vertebral artery. Residual or recurrent RDD lesions are generally sensitive to radiation therapy; therefore, stereotactic radiosurgery and traditional low-dose fractionated radiotherapy can be offered as adjuvant treatment options.[16] Petzold et al.[17] reported successful treatment of a recurrent RDD sellar mass with low-dose (20 Gy over 10 fractions) radiotherapy.[17] Two patients at Johns Hopkins Hospital treated with adjuvant radiotherapy for intracranial and spinal RDD showed improvement of their neurologic symptoms and disappearance of the targeted lesions.[16] A residual petroclival lesion extending into the left cavernous sinus responded well to adjuvant stereotactic radiosurgery 2 months after resection.[18] In the largest case series of 6 patients diagnosed with CNS RDD, 4 patients received adjuvant radiation therapy, but intramedullary spinal cord lesion failed to respond.[7] Adjuvant radiation therapy for RDD located in the foramen magnum has never been attempted before. Chemotherapy has a limited role in the treatment of CNS RDD. Genomic studies on RDD will help us better understand the molecular basis of the disease. Recently, next-generation sequencing of RDD of the CNS with extensive involvement of the midbrain, pons, and medial temporal lobe identified a single somatic pathogenic mutation in exon 12 of the BRAF gene: c.1457-1471del (p.486-491del).[19] Another case of BRAF V600E mutation was also reported in the literature. BRAF is a homodimer of the MAP kinase pathway which is involved in cell proliferation and cancer in melanoma and other tumors of the CNS.[20,21] Mutated BRAF continuously stimulates the MAP kinase pathway independently of regulated growth factor. In addition to that, KRAS mutations were also identified in the base of the skull in resected RDD.[22] These molecular findings suggest that inhibitors of the MAP kinase pathway and other targeted therapies may be effective in RDD.

CONCLUSIONS

RDD in the CNS is a rare condition that should be considered on the differential diagnosis of dural-based lesions

Table 1. Cranio Cervical Rosai Dorfman Cases

Study	Age (years)/ Sex	Clinical Presentation	Neuroimaging findings	Location	Surgery	Pathology	Adjuvant Therapy	Follow-Up
Tubbs et al., 2005[6]	13/M	Neck pain	Brain/C-spine MRI: enhancing mass	Cervical spine	Lesion biopsy	Diffuse staining for S-100 protein in the histiocytes	6-mercaptopurine and methotrexate	After 1 year, stable condition
Ambekar et al., 2011[8]	37/F	Visual symptoms: visual acuity of 6 of 9 and primary optic atrophy in both eyes Asymmetric spastic quadriparesis with graded sensory loss below C6	Brain MRI: T1-weighted isointense mass lesion T2-weighted hypointense and enhancing intensely on Gd contrast	Foramen magnum, extending to T2 and anteriorly along the clival dura up to the clinoids	Midline suboccipital craniectomy and tumor resection	Emperipolesis; aggregates of lymphoplasmacytic cells with foamy histiocytes and giant cells CD68+, S100+, CD1a−	Radiation therapy	-
Maiti et al., 2011[12]	19/F	Neck pain, spastic quadriparesis, hypertonia, weakness 2 of 5	MRI: isointense in T1- and T2-weighted, with homogenous contrast enhancement	Extradural lesion at C3-6	C2-6 laminectomy and excision of the extradural lesion	Aggregates of lymphocytes and histiocytes; emperipolesis, CD68+, S100+, CD1a−	-	After 1 year, doubtful residue/recurrence opposite C4
Xin et al., 2016[13]	40/M	Neck pain, paraparesis (4 of 5 LE)	Spine MRI: T1-weighted and T2-weighted homogeneously isointense—homogenous enhancement after Gd Dural tail at ventral dura	C3-5 and C6-7	C3-6 laminectomy and resection of both intradural lesions	Emperipolesis, CD68+, S100+, CD1a−	-	After 2 years, improvement of neurologic symptoms; no new complaints
Khartigeyan et al., 2017[14]	21/M	Spastic quadriparesis with grade 1—2 of 5 in all limb	MRI: dural-based mass, T1-weighted isointense, T2-weighted mildly hyperintense, and homogeneously enhancing with Gd	Cervicomedullary junction	Piecemeal tumor resection	Histiocytes with abundant amphophilic cytoplasm emperipolesis; CD68+, S100+, CD1a−	-	After 6 months, no residual tumor or recurrence
de León et al., 2017[15]	28/M	Tetraparesis (4+ of 5 LUE and LLE; 3 of 5 proximal and 1—2 of 5 distal RUE tactile hypoesthesia and hypoalgesia in the right C5-8 territories	Brain MRI: postcontrast cervical T1-weighted sagittal sequence displaying intense homogeneous contrast uptake T2-weighted: paranasal sinus obliteration and heterogeneous signal hyperintensities	Craniocervical junction and extending from the foramen magnum to C2	Cervical spinal cord decompression with suboccipital craniectomy for complete tumor resection		Oral corticosteroids	After 4 years, no neurologic symptoms, no extranodal lesion

M, male; MRI, magnetic resonance imaging; F, female; Gd, gadolinium; LE, lower extremity; LUE, left upper extremity; LLE, left lower extremity; RUE, right upper extremity.

suspicious of a meningioma. Radiologic features that are predictive of RDD are still elusive. Histologic analysis and immunostaining studies are essential to establish a definitive diagnosis of RDD. Surgery should be performed for diagnostic purposes and for the relief of neurologic compression, along with stereotactic fractionated radiation therapy or stereotactic radiosurgery being used for the general treatment of the disease. Future genomic studies will help us understand the pathogenesis of the disease and the use of novel adjuvant targeted treatments.

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