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ROSAI-DORFMAN DISEASE PRECEDING ACUTE MYELOID LEUKEMIA: AN EXTREMELY RARE CASE AND A LITERATURE REVIEW

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ABSTRACT

Background: Rosai-Dorfman disease (RDD) is a histiocytic disorder that was recently reclassified as a histiocytic neoplasm. It is characterized by nodal and extranodal involvement. Leukaemia-associated RDD is a rare subtype of neoplasia-associated RDD, particularly when leukaemia precedes RDD, with only one paediatric case reported in the literature.

Case report: A 33-year-old woman presented with cervical swelling that had persisted for one month. Ultrasound examination and biopsy confirmed the diagnosis of RDD. The patient subsequently developed raccoon eyes and bilateral eyelid oedema. Laboratory investigations revealed bicytopenia and leukocytosis. Unexpectedly, bone marrow aspirate and flow cytometry confirmed the presence of acute myeloid leukaemia (AML). Following repeated complaints of headache, brain magnetic resonance imaging revealed a callosal lesion, suggestive of a space-occupying lesion. One year later, the patient relapsed and died from septicaemia.

Conclusion: This case report describes the progression of RDD to AML in an adult, highlighting the need for long-term follow-up and further research into its pathogenesis to improve outcomes.

KEYWORDS

Rosai-Dorfman disease, acute myeloid leukaemia, neoplasia-associated RDD, histiocytosis

LEARNING POINTS

- The occurrence of Rosai-Dorfman disease (RDD) followed by acute myeloid leukaemia is extremely rare, suggesting more than a coincidental link and providing a foundation for research into RDD pathophysiology and prognosis.
- Physicians should be aware of the potential progression of RDD to malignancy, even after complete remission, and ensure thorough follow-up for early detection.

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INTRODUCTION

Rosai-Dorfman disease (RDD) is a rare form of non-Langerhans cell histiocytosis (non-LCH)[1]. Its aetiology is not yet well understood; however, mutations in the RAS/RAF/MAPK pathway have been described in some cases. It is classified into three categories: sporadic noncutaneous, familial, and cutaneous[1]. It is characterized by nodal involvement and extranodal involvement in more than 40% of cases[2]. Extranodal involvement includes the nasal cavity, orbital tissue, skin, bone, and central nervous system (CNS), in decreasing order of frequency[2].

Clinically, patients with RDD typically present with bilateral cervical lymphadenopathy and B-symptoms, which include fever, night sweats, and weight loss, along with other symptoms related to the affected extranodal organs[3]. Some cases of RDD have been found to be associated with neoplasia, referred to as neoplasia-associated RDD, including Hodgkin and non-Hodgkin lymphomas. RDD has also been observed following myelodysplastic syndrome in some cases[4]. Although leukaemia is un not commonly related to RDD, it usually precedes and potentially triggers the onset of RDD or occurs simultaneously, making the occurrence of leukaemia following RDD extremely rare[5].

In this instance, we present the case of an adult with RDD followed by acute myeloid leukaemia (AML), detailing the full clinical course.

CASE DESCRIPTION

A 33-year-old female with neck swelling presented to the hospital. Neck examination revealed bilateral enlarged cervical lymph nodes. Her laboratory parameters, including a complete blood count, were normal, except for an elevated erythrocyte sedimentation rate (ESR) (60 mm/hr; normal up to 10 mm/hr). A neck ultrasound revealed multiple significantly enlarged, suspicious cervical lymph nodes, with the largest on the right side measuring 4.6 × 2 cm and the largest on the left side measuring 3 × 1.9 cm.

An excisional cervical lymph node biopsy was performed. Pathologic examination revealed marked sinus expansion by distinctive large histiocytes with round nuclei and prominent nucleoli, surrounded by abundant pale cytoplasm with poorly defined borders and evident emperipolesis. The results suggested the diagnosis of RDD, supported by a strongly positive reactivity for both S100 protein and CD68 in the histiocytes *(Fig. 1)*, and negative reactivity for CD10, CD30, and CD1a, with a mixed population positive for CD3 and CD20 in a reactive pattern in the cells between the sinuses. The results of the bone marrow examination and biopsy were unremarkable. A whole-body computed tomography (CT) scan revealed bilateral enlarged axillary and external iliac lymph nodes, in addition to the cervical lymph nodes. The patient started chemotherapy with 100 mg/m^2 etoposide in conjunction with 8 mg dexamethasone every 12 hours for 3 days every 3 weeks. During one of the follow-up appointments, the patient reported experiencing recurrent severe headaches. A brain CT scan was performed, revealing a fairly well-defined hyperdense lesion located midline in relation to the corpus callosum *(Fig. 2)* accompanied by nasal septal soft tissue masses *(Fig. 3)*. To further evaluate the lesion, magnetic resonance imaging (MRI) was performed, confirming the presence of a well-defined callosal mass *(Fig. 4)*. However, the nature of the lesion could not be

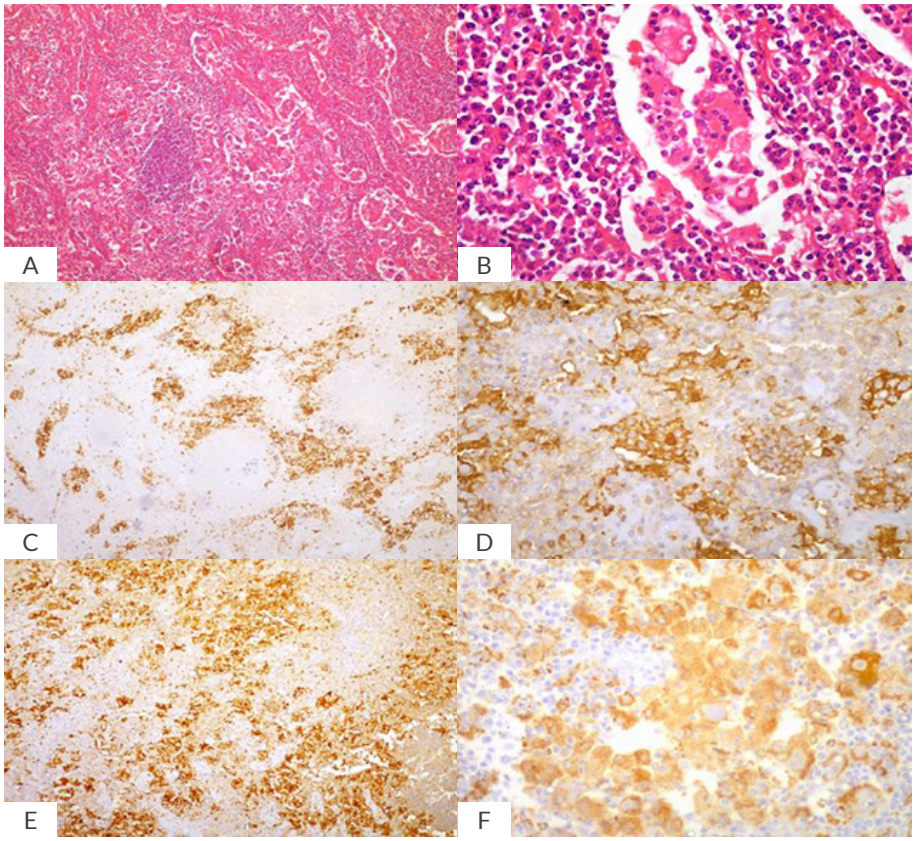


Figure 1. Histological findings. A) Lymph node with marked sinus expansion by multiple large histiocytes, (H&E ×100); B) The histeocytes possess round nuclei and prominent nucleoli, surrounded by abundant pale cytoplasm with poorly defined borders with evident emperipolesis(H&E ×400); C) Immunohistochemistry for S100 highlights numerous histiocytes within nodal sinuses (IHC ×100); D) S100 stains the characteristic histiocytes of Rosai–Dorfman disease, showing emperipolesis of numerous intact lymphocytes (IHC ×400); E) Immunohistochemistry for CD68 shows wide spread histeocytes in the nodal sinuses (IHC ×100); F) Highlighted CD68 positive histeocytes with emperipolesis (IHC ×400).

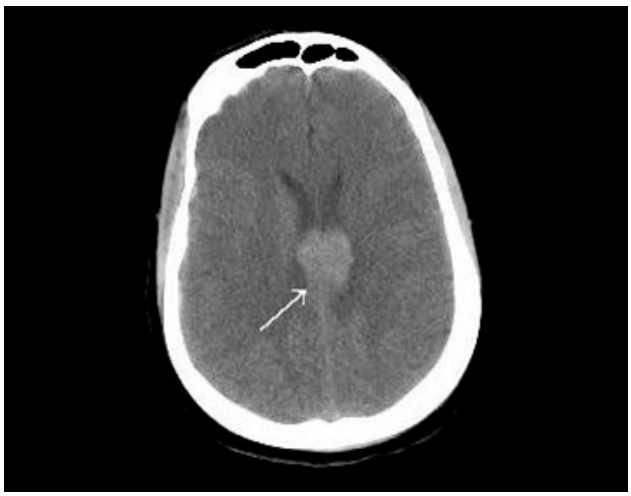


Figure 2. A non-contrast computed tomography scan of the brain revealed a well-defined hyperdense lesion measuring 16.8 × 10.7 mm at the midline in relation to the corpus callosum (arrow). The ventricular system is normal in size and configuration, with no evidence of a midline shift.



Figure 3. A non-contrast computed tomography scan of the paranasal sinuses reveals soft tissue masses related to the nasal septum without bone destruction (arrow).

determined, as the patient refused surgical resection.

After 6 months of treatment, there was a residual submental lymph node of 1.3 cm, which showed reactive hyperplasia on biopsy. The patient then had follow-up for 18 months, after which she experienced relapse with enlarged neck lymph nodes. Re-excision confirmed RDD. She received methotrexate (1 mg) on day 1 and cytarabine (200 mg) on days 1-3 every 4 weeks for 3 cycles. However, non-contrast CT scan revealed a markedly regressive course of the previously mentioned corpus callosal lesion *(Fig. 5)*.

She then went into remission and continued follow-up for 4 months until she presented to the hospital with raccoon eyes. Her laboratory investigations revealed an abnormal CBC with leukocytosis and bicytopenia, as well as elevated fibrin degradation products, D-dimer, and lactate dehydrogenase levels *(Table 1)*. Acute promyelocytic leukaemia was suspected, and we started all-trans retinoic acid (ATRA). Bone marrow aspirate and flow cytometry revealed blast cells that were positive for CD34 (partial dim 27.3%), CD81, CD58, CD13, CD117 (dim to negative), CD33, CD64, MPO, and negative for CD10, CD19, CD20, CD38, HLADR, CD36, CD14, cCD79a, cCD3, TdT, cCD22, supporting the diagnosis of AML M3. t(15;17) and inv(16) were positive as well.

The patient continued ATRA with dexamethasone and a 3-day regimen of doxorubicin, as well as transfusion support. A bone marrow assessment after 3 weeks revealed 10% promyelocytes, while the bone marrow biopsy was unremarkable. She continued ATRA, and a bone marrow assessment 2 months later revealed remission. Promyelocytic leukaemia/retinoic acid receptor alpha (PML-RARA) was not available. She then started maintenance ATRA (45 mg/m^2 for 2 weeks every 3 months), methotrexate (20 mg/m^2 once weekly), and 6-mercaptopurine (2 tablets daily). Unfortunately, 1 year later, she relapsed and died of septicaemia.

DISCUSSION

RDD is a rare, self-limited histiocytic neoplasm with a poorly identified aetiology[3]. Histological analysis of RDD typically

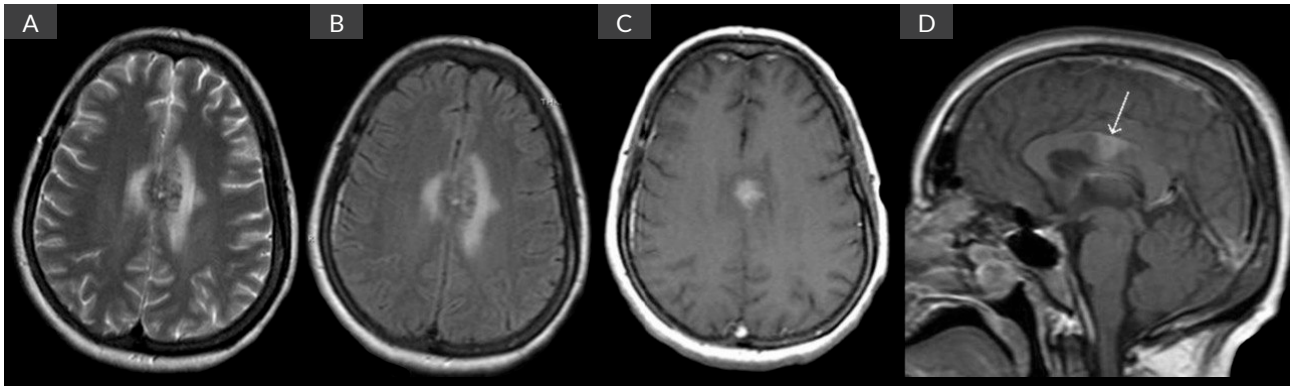


Figure 4. Imaging findings. A) Magnetic resonance imaging of a T2-weighted axial cut of the brain revealed a well-defined callosal mass lesion displaying an intermediate signal surrounded by mild perifocal oedema; B) A fluid-attenuated inversion recovery image axial cut showing the mentioned lesion and the related oedema; C, D) Postcontrast T1-weighted axial and sagittal images sequentially demonstrated that the callosal lesion (arrow) displayed mild to moderate homogeneous enhancement. Additionally, mild leptomeningeal thickening and enhancement were observed in both the frontal and right temporoparietal regions.

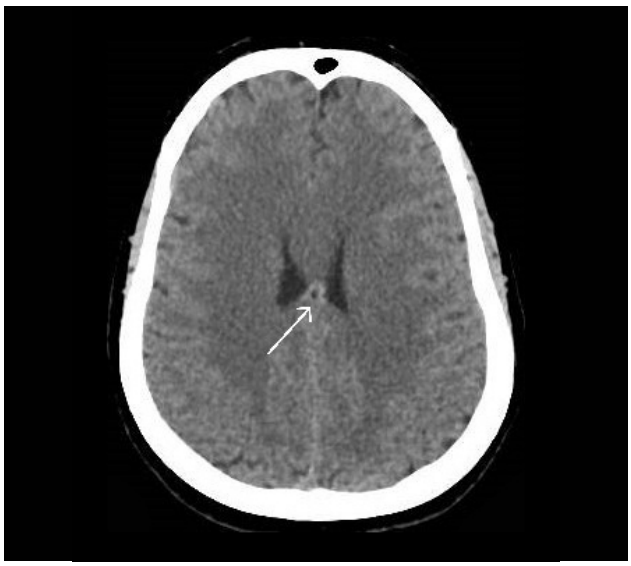


Figure 5. A non-contrast CT scan of the brain revealed a regressive course of the callosal lesion, which nearly resolved (arrow).

reveals pericapsular fibrosis and dilated sinuses densely infiltrated by large histiocytes, lymphocytes, and plasma cells. With emperipolesis as the most unique feature of histiocytes[3]. A hallmark diagnostic feature is the presence of S-100-positive histiocytes that engulf lymphocytes and plasma cells. Immunohistochemical staining usually reveals that RDD cells are positive for CD68 and CD163 but negative for CD1a and CD207 (langerin). Genetic sequencing is limited to treatment-resistant cases[6].

When studying the clonal predisposition to RDD, mutations in the MAPK/ERK pathway have been found in 30 to 50% of cases, alongside several genetic mutations, such as SLC29A3, KRAS, ARAF, NRAS, and MAP2K1. Notably, KRAS and MAP2K1 mutations have been identified in 33% of RDD patients, suggesting that some subsets of RDD patients may be clonal[2]. Additionally, BRAF V600E mutations have been identified in some cases[2].

The most prominent clinical manifestation of RDD is nodal involvement, typically presenting as bilateral cervical lymphadenopathy. However, extranodal manifestations are observed in approximately 43% of cases. These include the skin (10%), nasal cavity (11%), bone (5–10%), and rarely, the CNS (5%)[2,7]. In our patient, nodal involvement along with nasal sinus involvement was observed, and intracranial RDD could not be ruled out. Although the involvement of the paranasal sinuses is typically self-limited and expected to remit spontaneously, surgical removal may be necessary if functional disorders occur. However, recurrence after surgical resection remains a concern[8,9]. Notably, patients with maxillary sinus involvement tend to have a relatively poor prognosis[8]. In rare instances, isolated paranasal sinus RDD without nodal involvement has been documented[8].

On the other hand, CNS involvement is rarely observed in RDD patients, with approximately 90% intracranial lesions and rarer involvement of the spinal canal[10,11]. The symptoms are highly variable according to the site of involvement, and headache, epilepsy, and focal neurological deficits are the common symptoms associated with intracranial RDD. Spinal RDD usually causes compression and subsequent sensory and motor dysfunction[11,12]. MRI findings of intracranial RDD are often inconclusive and frequently misdiagnosed as meningioma due to the similar MRI characteristics of dura-based lesions. On T1-weighted MRI, intracranial RDD

Test	Result	Reference range
Complete blood count		
White blood cell count (×10³/µl)	24.8	4.1-11
Red blood cell count (×10⁶/µl)	2.97	4.2-6.3
Haemoglobin (g/dl)	7.91	12-18
Platelets (×10³/µl)	19.3	140-440
Neutrophils (×10³/µl)	0.575	2-7.8
Neutrophils (%)	2.32	37-92
Lymphocytes (×10³/µl)	9.25	0.6-4.1
Lymphocytes (%)	37.3	10-58.5
Blood chemistry		
Lactate dehydrogenase (U/l)	2062	100-190
Coagulation profile		
Fibrin degradation product	positive	negative
D-dimer (µg/ml)	7.3	<0.5

Table 1. Laboratory investigations.

typically appears as an isointense or hyperintense mass with well-defined borders. On T2-weighted MRI, it usually presents as an isointense lesion, necessitating biopsy for a definitive diagnosis. Surgical removal is the mainstay of treatment; radiotherapy, chemotherapy, and steroids have also shown benefits[13]. Our patient complained of a headache, and her MRI confirmed the presence of an intracranial (callosal) space-occupying lesion. However, the nature of the lesion was not confirmed, as the patient refused to undergo surgery.

Neoplasia-associated RDD is a newly identified subset of RDD, defined as RDD occurring before, simultaneously with, or after a malignancy[2,14]. Our review revealed that most leukaemia-related RDD cases involve leukaemia preceding or concurrently diagnosed with RDD[5]. This makes our case an extremely rare instance of leukaemia following RDD in adulthood. To date, we have identified 70 cases of neoplasia-associated RDD, with 15 patients (20%) having died, which is relatively high compared with the mortality rate of 10% among general RDD patients[2]. Among the 8 patients with leukaemia-related RDD, 4 patients (50%) died, indicating a potentially worse prognosis for neoplasia-associated RDD in general and leukaemia-associated RDD in particular. To our knowledge, no study has thoroughly investigated mortality rates in patients with neoplasia-associated RDD.

Currently, no standard treatment exists for RDD, and management should be individualized on the basis of the clinical situation[4]. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Histiocytic Neoplasms along with previously published consensus recommendations, have proposed treatment approaches for RDD[2,4,15]. Generally, a watch-and-wait strategy is useful for asymptomatic, uncomplicated, unifocal, and multifocal cases. Surgical treatment is effective for unifocal, resectable, symptomatic, and complicated lesions. Systemic therapies are indicated for multifocal symptomatic disease[3,15]. Targeted therapies such as the BRAF inhibitor vemurafenib or dabrafenib and the MAP/kinase inhibitors cobimetinib, trametinib and binimetinib are the treatments of choice if mutations are present. Targeted therapies against rare mutations, such as NTRK, ALK or RET, can also be given in mutated cases. Chemotherapeutic agents such as cytarabine, cladribine, methotrexate and hydroxyurea have shown variable responses in RDD[3,4]. Whenever a patient developed leukaemia-associated RDD, as in our case, the treatment plan was according to the leukaemia algorithm.

CONCLUSION

This case report highlights a rare instance of an adult developing AML following RDD. The clinical course appears to be more than coincidental. Even after complete remission of RDD, physicians should remain mindful of this potential progression and ensure thorough follow-up to detect any subsequent malignancies early. Our case contributes to the growing body of evidence that leukaemia-associated RDD potentially has a poorer prognosis than typical RDD does. Future research should explore the underlying genetic causes and pathogenesis to better understand this complexity, design effective treatment protocols, and improve overall patient outcomes.

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