—Case Reports—

A Rare Case of Extra-Nodal Rosai-Dorfman Disease of the Cheek

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Rosai-Dorfman disease (RDD), which was first reported by Rosai and Dorfman in 1969, is a rare, benign, non-neoplastic proliferation of histiocytes, characterized by painless lymphadenopathy and fever. Lymphadenopathy occurs most commonly in the neck, but also appears in non-cervical lymph nodes or as extranodal lesions. In this case, biopsy of an atypical subcutaneous buccal mass, which was difficult to diagnose preoperatively, led to a diagnosis of RDD. In addition, although lesions were also confirmed in the maxilla, none of the lesions were in lymph nodes; therefore, we ultimately diagnosed the patient with extranodal RDD (ENRDD). Compared with classical RDD, characterized by painless lymphadenopathy and fever, ENRDD is observed only in soft tissue and bone, and occurs mostly frequently among older adults. Cases presenting with lymph node or vital organ lesions also present with systemic symptoms, usually with a progressive and sometimes fatal course. However, RDD localized in soft tissue and bone has a favorable prognosis, and follow-up alone is considered sufficient. Although this case featured epidemiological characteristics of ENRDD, and as there are no fixed therapeutic guidelines, the recommendation is that treatment be considered on a case-by-case basis according to the site and symptoms. There are few reports of ENRDD; therefore, we aim to contribute the details of an additional case to the literature. (J Nippon Med Sch 2024; 91: 502–507)

Key words: Rosai-Dorfman disease, extra-nodal Rosai-Dorfman disease, soft tissue of Rosai-Dorfman disease, bone of Rosai-Dorfman disease, mesenchymal tumor

Introduction

Rosai-Dorfman disease (RDD), which was first reported by Rosai and Dorfman in 1969, is a rare, benign, non-neoplastic proliferation of histocytes characterized by painless lymphadenopathy and fever[1]. In addition to lymph nodes, RDD also occurs in extranodal organs; along with the skin and central nervous system, a small number of RDD cases have been reported in bone and soft tissue. While 5-10% of RDD cases occur in bone, extranodal involvement is considered typical[2]. In this case, diagnostic imaging of an atypical subcutaneous mass in the cheek, which was difficult to diagnose preoperatively, could not rule out malignancy. Consequently, we performed radical biopsy, which led to the diagnosis of RDD. Despite additional symptoms indicative of RDD in the maxilla, there was no evidence of lymph node lesions, and the patient was ultimately diagnosed with extranodal RDD (ENRDD). Typically, ENRDD in bone or soft tissue without intranodal lesions has a favorable prognosis, and follow-up is considered sufficient[3]. However, few cases have been reported in the literature, and fixed therapeutic guidelines do not exist. In addition, epidemiologically, this case differed from typical RDD, which involves intranodal lesions and systemic symptoms. We therefore discuss our case in relation to the relevant literature.

Case Report

Chief complaint

A 57-year-old Japanese female presented with a subcutaneous mass in the left cheek.

Medical history

Basal cell carcinoma of the nose (surgery at 57 years old, stage I), hypertension, diabetes mellitus, deaf-

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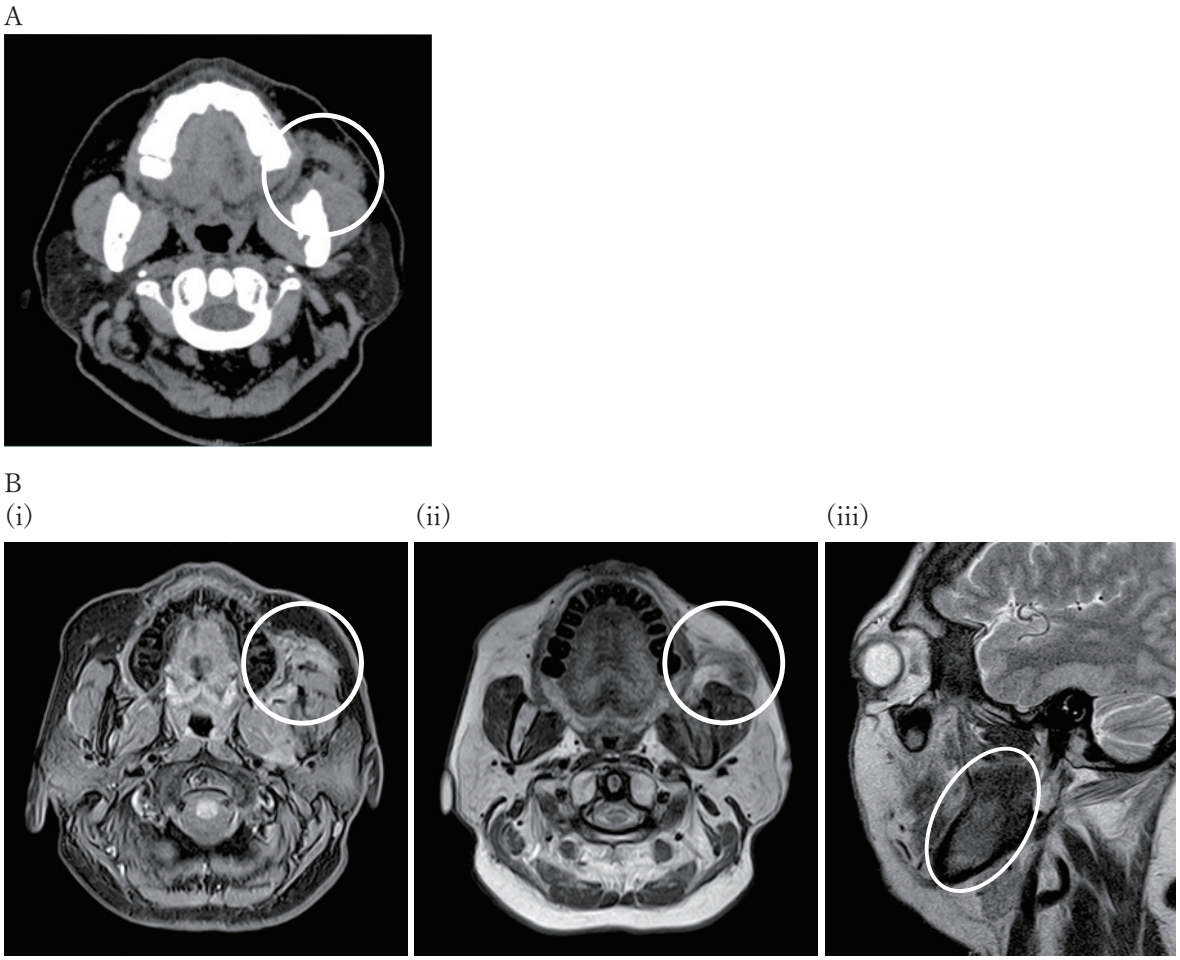

Fig. 1 High-permeability tumor shadow is visible in the masticator space. In plain CT, the CT value is similar to that of muscle (A). In a T1-weighted fat-suppressed image (Dixon method), the tumor shadow is hyperintense relative to adipose tissue (i). In a T2-weighted fat-suppressed image (Dixon method), the tumor shadow is somewhat hypointense (ii), (iii). Edema is present in the adjacent masseter and maxillary bone marrow (ii), (iii). Image searches with contrast could not be performed due to renal impairment.

mutism.

History of present illness

The patient perceived a mass below the left check several months prior to initial examination at our hospital but did not seek treatment. Basal cell carcinoma was discovered when the patient requested examination of the left cheek in a regular check-up.

Symptoms in initial visit

An elastic, hard mass was palpable below the left cheek with associated mild tenderness. No salivary colic was noted.

Laboratory test results

WBC 8,220/μL, Neut 74.5%, Lymp 16.5%, Mono 6.1%, Eosi 2.4%, Baso 0.5%, RBC 355×10^4/μL, Hb 9.9 g/dL, MCV 89.0 fL, Plt 295×10^3/μL, TP 7.3 g/dL, Alb 3.9 g/dL, BUN 23.3 mg/dL, Cre 1.48 mg/dL, eGFR 29.4, Na 141 mEq/L, K 4.4 mEq/L, Cl 108 mEq/L, LDH 195 U/L, AST 20 U/L, ALT 22 U/L, ALP116 U/L, CRP 0.09 mg/dL.

Plain CT (Fig. 1A)

High-permeability tumor shadow in the masticator space.

Plain MRI (Fig. 1B)

High-permeability tumor shadow with high signal intensity on a T1-weighted image and somewhat low signal intensity on a T2-weighted image. Involvement of bone marrow edema in the adjacent masseter and maxilla. Images with contrast could not be performed due to renal impairment.

Although preoperative diagnosis was complicated by a dearth of specific findings, the lesion was a high-permeability lesion extending from the buccal space to the masticator space. We performed open biopsy for malignancy with a primary lesion of the accessory parotid gland as the most likely diagnosis.

Operative findings (Fig. 2)

Surgery was performed under local anesthesia. The in-

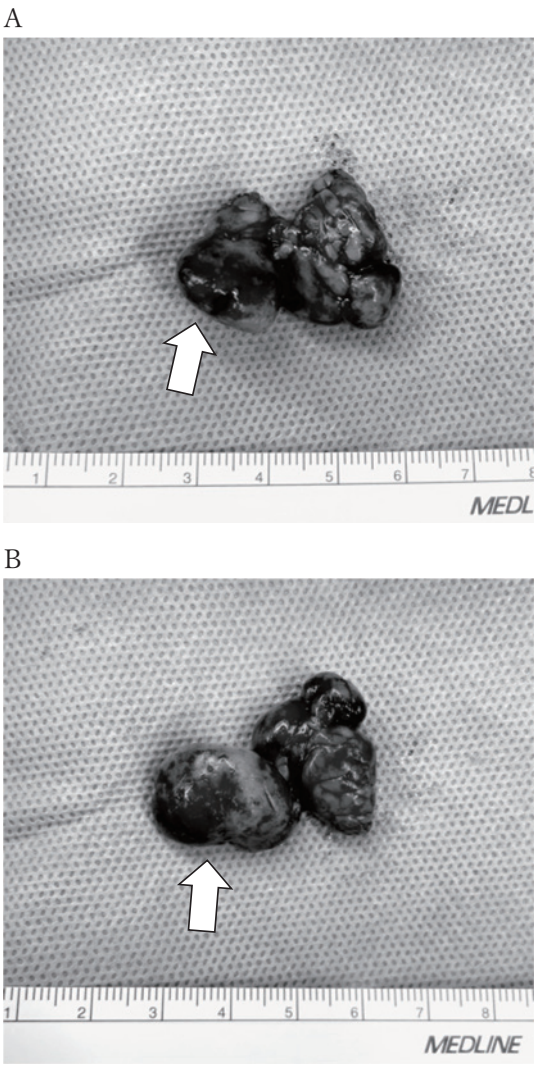

Fig. 2 Macroscopic images of the anterior (A) and posterior (B) of the resected specimen, which was 30 × 33 mm in size. Elastic and hard tissue, palpable through the skin (arrow) and soft tissue along the buccal space, was resected as a single lump. Both were well-defined and easily detached from the surrounding area.

cision was made directly above the identified mass. The mass was elastic, hard, well-defined, and extended in depth to be in contact with the masseter. When the mass was bluntly detached, it was well-defined and detached easily along the buccal space. Since the tumor was enucleated from a microincision without further incision, we performed radical biopsy.

Histopathological findings (Fig. 3)

The mass (arrow in A) featured diffuse infiltration of histiocyte-like cells, lymphocytes, and plasma cells, as well as fibrosis. Continuous soft tissue included a high volume of adipose tissue, but the interspersed solid portion demonstrated similar cell infiltration. A medium-power view (B) showed diffuse or aggregated pale eosin-stained histocyte-like cells with large-volume cytoplasm, as well as infiltration by large numbers of lymphocytes and plasma cells. In a high-power view (C), pale eosin-stained histiocyte-like cells with large-volume cytoplasm were noted to contain lymphocytes and plasma, having been endocytosed without degeneration (emperipolesis) (arrows). In immunostaining, nearly all large histiocytic cells were S-100 protein positive. CD68 was positive only in some histiocytic cells, while CD1a was negative.

Based on the above findings, we diagnosed the patient with RDD.

Course

Buccal lymph nodes are a type of facial lymph node in the buccal space, where a subcutaneous mass was present in our case. As the biopsied specimen did not demonstrate a lymph node structure, we determined the mass to be an extranodal lesion. A whole-body CT scan from neck to the pelvis did not reveal any significant lymphadenopathy or nodular lesions. A total 5-10% of RDD cases involve the bones[2], therefore, we re-examined the edematous changes in the left maxillary bone marrow approaching the masseter that were observed on preoperative MRI. The patient had no caries. The lesion center was separated from the wisdom tooth and extensive. This is atypical for infection-related osteomyelitis, and an RDD-associated lesion was suspected. Due to the potential for renal impairment associated with RDD[4], we discussed the case with the doctors from the department of nephrology. The patient was negative for urine protein and occult blood, urine protein quantification was ≤ 10 mg/dL, and urinary cre was 32.9 mg/dL: abnormal findings were absent. In addition, CT revealed mild renal atrophy. Therefore, we diagnosed the patient with chronic renal failure secondary to hypertension and diabetes mellitus.

Definitive diagnosis

Extranodal RDD (ENRDD).

Discussion

Histiocytosis is a rare disease characterized by the accumulation of histiocytes, such as monocytes, macrophages, and dendritic cells, in various tissues and organs throughout the body. While there are over 100 subtypes, in 2016, the Histocyte Society classified histiocytosis into five groups; "C" group: cutaneous and mucocutaneous histiocytoses; "M" group: malignant histiocytosis; "R" group: Rosai-Dorfman disease (RDD) and miscellaneous noncutaneous, non-Langerhans cell histiocytosis; and

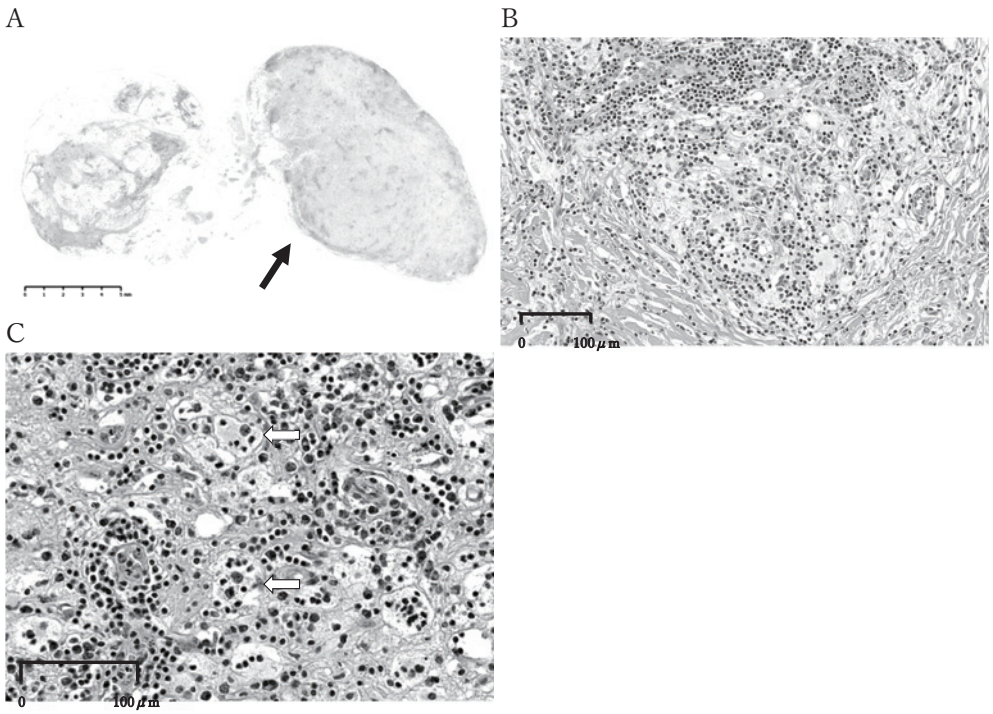

Fig. 3 Elastic and hard portions of the solid mass (arrow in A) demonstrate diffuse infiltration by histiocyte-like cells, lymphocytes, and plasma cells as well as fibrosis. The soft tissue contains a high volume of adipose tissue, while the solid portion demonstrates similar interspersed cell infiltration. Medium-power view (B) shows diffuse or aggregated pale eosin-stained histocyte-like cells with large-volume cytoplasm, as well as infiltration by a large number of lymphocytes and plasma cells. High-power view (C), lymphocytes and increased plasma volume are observed within pale eosin-stained histiocyte-like cells with large cytoplasm-volume.

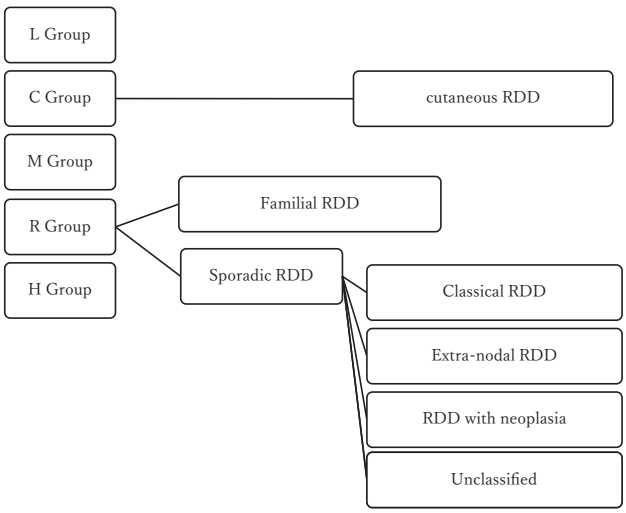

Fig. 4 Classification of histiocytosis[5]
RDD, Rosai–Dorfman disease

"H" group: hemophagocytic lymphohistiocytosis and macrophage activation syndrome. The classification is based on histology, phenotype, molecular alterations, and clinical/imaging characteristics. The R Group is divided into familiar and sporadic RDD, with the latter further divided into classical, extranodal, neoplastic or immune-mediated, and unclassified (**Fig. 4**)[5]. Cutaneous RDD, a variant of ENRDD, demonstrates unique epidemiological and clinical characteristics and is classified into the C Group; therefore, cutaneous RDD is considered a separate disease. Histopathologically, RDD is characterized by the proliferation/deposition of histiocytes with cytoplasm containing lymphocytes and erythrocytes without degeneration (emperipolesis)[1]. In immunostaining, RDD is positive for S-100 protein and CD68, but negative for CD1a, which differs from Langerhans cell histiocytosis. Although the cause of RDD has not yet been determined, viral infection, such as human herpesvirus 6[6,7], Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus[8], is thought to be involved. There are also reports of association with malignant lymphoma[9], cases with comorbid myelodysplastic syndrome[10], and onset following bone marrow transplantation[11]. Tumors are also presumed to be associated with RDD, with reports of mutations in NRAS, KRAS, MAP2K1, and ARAF[12].

Rosai-Dorfman disease is a rare condition with a prevalence of 1:200,000 and roughly 100 novel cases annually in the United States[12]. The mean age of onset is 20.6 years with 62% of cases occurring under the age of 10 and 81% developing symptoms under the age of 20[13]. Extranodal lesions are recorded in 43% of cases, with the most common sites being the skin, nasal cavity, bone, soft tissue, and retro-orbital tissue[14]. Bone involvement occurs in 5-10% of cases[2]. The mean ages of patients with ENRDD with soft tissue lesions and bone lesions are 42.5-46 years and 31 years, respectively[15]. The mean age of patients developing ENRDD of the head and neck is 38 years[16]. The average age of ENRDD onset in any of these sites is higher than that for RDD. Overall, RDD is slightly more common in men than in women, with a sex ratio of 1.33:1[17]; however, RDD in bone, soft tissue, and skin is slightly more common in women[2,12]. In terms of race, RDD occurs most often in African Americans and Caucasians; although RDD overall is not common in Asians, cutaneous RDD is reported to be common in Asians[12]. The patient in this case is Japanese; bone involvement is reported to occur in 8.8% of cases of RDD in Japan, a figure consistent with previous studies[18]. However, no studies have compared racial differences in RDD of the soft tissues and bone; therefore, additional case reports are required. In one study, 80 of 93 patients (74.1%) with bone lesions demonstrated extranodal lesions, most commonly occurring in the soft tissue (n = 27). These findings reveal a tendency for comorbid lesion development in the bones and soft tissue. The most common bone lesion sites were in the skull (n = 33) and the facial bones (n = 24)[15]. According to this, the patient in this case, who was a relatively older woman, developed ENRDD of the face; these trends are characteristic of ENRDD localized in soft tissue and bone, and are similar to the trends reported in previous studies.

The typical symptoms and prognosis of RDD differ by subtype. Classical RDD, which can be sporadic or familial, is typified by bilateral painless cervical lymphadenopathy with fever, weight loss, and night sweats[4]. Although many cases remit spontaneously following a long-term course and have a favorable prognosis, RDD can be progressive and fatal in patients who demonstrate wide-ranging nodular lesions or lesions in vital organs such as the kidneys or liver. Treatment is primarily surgical, with surgery selected in most cases[19]. Steroids and radiotherapy may be effective, and some reports suggest chemotherapy with antimetabolites (cladribine, vinblastine, methotrexate, 6-mercaptopurine) and the molecular targeted drug rituximab can be effective[19]. Soft tissue RDD involves pain in 16.8% of cases, but most cases are painless[17]. Our patient was also asymptomatic. She requested a medical examination for basal cell carcinoma during a regular consultation, and the diagnosis was made as a result of a close examination. Although the main symptoms of RDD with bone involvement are pain and swelling, RDD may remain painless and be discovered incidentally in radiological imaging[20]. The bone lesion in this case was also asymptomatic and incidentally discovered on radiological imaging. Although prognosis is reported to be poor in patients with soft tissue and bone lesions and associated systemic symptoms, bone and soft tissue RDD typically has a favorable prognosis. As the course is often self-limiting, with frequent spontaneous lesion regression, follow-up is considered sufficient in patients with focal lesions[3]. In this case, we decided follow-up alone was the best treatment option. There was no recurrence of soft tissue lesions at 4 months after surgery, and the patient's bone lesion will be followed up regularly by imaging.

Rosai-Dorfman disease is a rare form of histiocytosis which is seldom suspected preoperatively when lymph node lesions are absent. Painless, focal ENRDD often does not require treatment. However, clinical diagnosis is difficult, and differentiation from malignancy frequently poses a problem; therefore, a biopsy should be performed. The possibility of RDD as a differential diagnosis should be considered for atypical masses/tumors in the head and neck region.

Conclusion

We report a case of ENRDD localized to an area ranging from the buccal soft tissue to the maxilla. Compared to classical RDD, the patient was a relatively older woman with localized facial lesions and no systemic symptoms; these observations are consistent with previous reports on RDD. In terms of race, RDD is most common in African-Americans and Caucasians, while cutaneous RDD is common in Asians. No study has yet compared racial differences in bone or soft tissue ENRDD; therefore, further investigation involving more cases is necessary.

Conflict of Interest: The authors declare no conflicts of interest.

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