



Radiotherapy for steroid-resistant laryngeal Rosai–Dorfman disease

D. Toguri MEng, A.V. Louie MD,† K. Rizkalla MD,‡ J. Franklin MD,§ G. Rodrigues MD MSc,† and V. Venkatesan MBBS†*

ABSTRACT

Rosai–Dorfman disease is a rare lymphoproliferative disorder that can have nodal and extranodal manifestations. In the absence of established guidelines for the management of this condition, various therapeutic modalities are used, including radiotherapy. Radiation dosages and fractionation schedules have not been reported in all instances. We present a case in which glottic and subglottic Rosai–Dorfman lesions causing airway obstruction in a frail steroid-refractory patient were put into complete remission using radiotherapy. The lesions responded transiently to a course of prednisone, but responded completely to external-beam radiation, with minimal side effects to the patient.

KEY WORDS

Rosai–Dorfman disease, histiocytosis with massive lymphadenopathy, radiotherapy

1. INTRODUCTION

Currently, there are no clear guidelines on the management of Rosai–Dorfman disease (RDD). Radiotherapy has been one of various therapeutic modalities used in the treatment of RDD, but there is a paucity of information describing the radiotherapy technique, dose, and fractionation, and the relative success of its use. Furthermore, advances in the delivery of external-beam radiation warrant the reporting of recent radiotherapeutic approaches to the management of RDD. Here, we contribute a case in which RDD of the larynx was put into complete remission with radiotherapy.

2. CASE DESCRIPTION

A 92-year-old woman presented with progressive stridor, exertional dyspnea, massive bilateral lymphadenopathy, and a nasopharyngeal mass. She was

referred to an otolaryngologist by her family physician. Flexible laryngoscopic examination revealed glottic and subglottic lesions with significant airway obstruction [Figure 1(A)]. Multiple biopsies of the nasopharyngeal mass revealed nonspecific ulceration and a mixed inflammatory reaction. A subsequent open biopsy of a submandibular lymph node facilitated a pathology diagnosis: sinus histiocytosis with massive lymphadenopathy, RDD. The lymph node was encased in a thickened, fibrous capsule. Paracortical regions of the nodes were expanded, and the follicles containing germinal centers were reduced in number [Figure 2(A)]. Emperipolesis, a classic microscopic feature of RDD, was observed [Figure 2(B)]. Immunohistochemistry staining revealed histiocytes positive for CD68, CD163, and S-100 expression [Figure 2(C)].

Oral prednisone 20 mg daily was prescribed, and respiratory symptoms resolved within 1 week. The patient subsequently achieved a complete response clinically and radiologically, and the steroids were tapered 4 months from the initial consultation. However, 2 months later, the woman returned to clinic with worsening respiratory distress. A pulse dose of steroids was administered and quickly weaned. This treatment provided brief relief of her symptoms, but stridor and exertional dyspnea recurred quickly. These symptoms were being caused by a residual subglottic mass. A referral to radiation oncology was made to alleviate the need for high-dose steroids in this elderly patient.

The patient's age and frail condition, together with social factors, precluded a lengthy fractionation regime. The goal was to give a long period of symptom control while being mindful of the potential toxicity for organs at risk, given that RDD is a benign condition. In this disease, the role of dose and fractionation selection is not known and cannot be elucidated through traditional methods of clinical trial. Ultimately, treatment should try to achieve durable disease control, but not at the expense of commonly accepted safe dose levels for organs at risk.

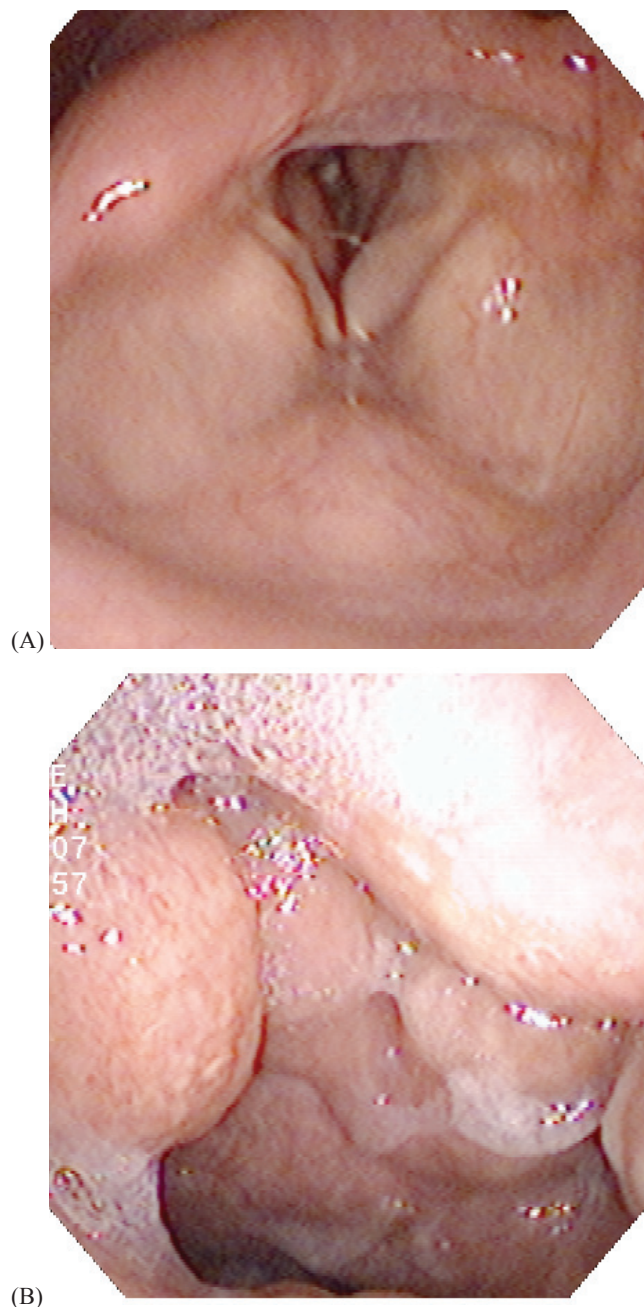


FIGURE 1 Images obtained by flexible laryngoscopy: (A) right-sided vocal cord lesion causing asymmetrical vocal cord movement; (B) exophytic nasopharyngeal mass.

The foregoing factors were considered in planning the total radiation dose and number of fractions eventually used: 25 Gy in 10 fractions, with a boost of 5 Gy to the gross tumour volume delivered in 2 fractions [Figure 3(A,B)]. External-beam radiation was delivered using a 3-dimensional conformal approach, with posterior–anterior and right and left oblique and lateral beams.

The prescribed treatment was well tolerated with minimal acute toxicity: mild dysphagia and fatigue.

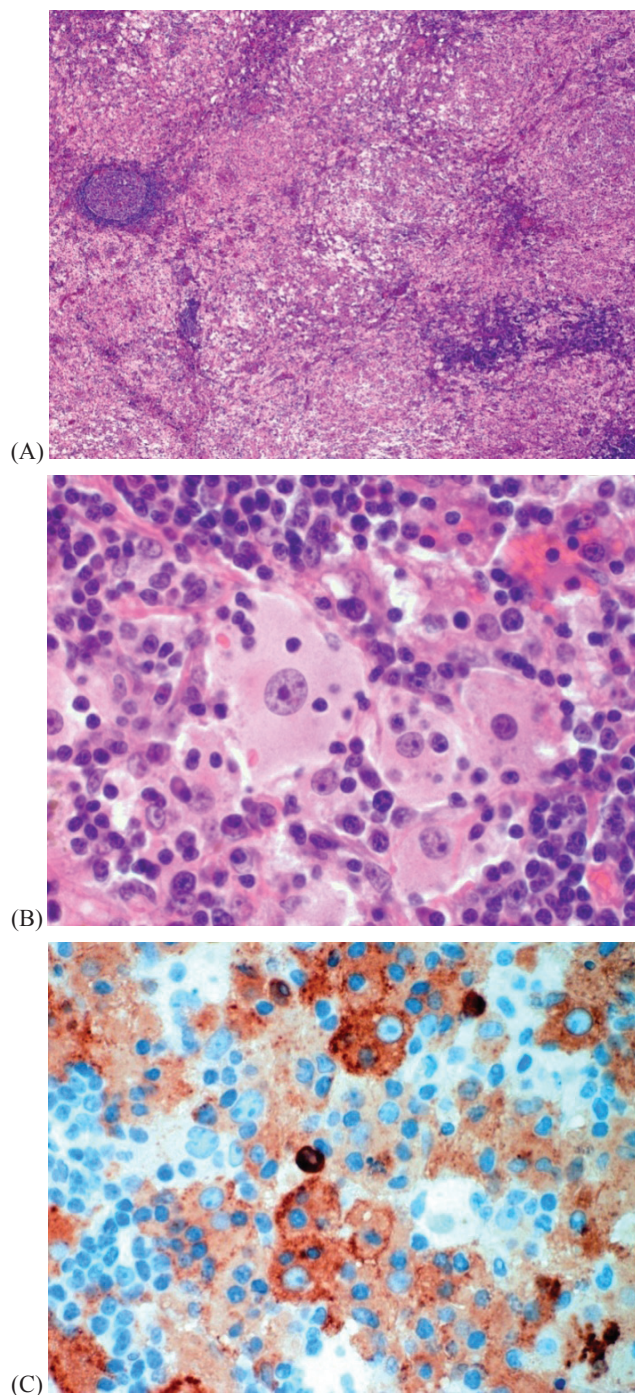


FIGURE 2 Histology micrographs demonstrating classical features of Rosai–Dorfman disease: (A) histiocytosis, expanded paracortex, and reduced number of follicles with germinal centers; (B) emperipolesis; (C) positive staining for the CD68, CD163, and S-100 immunophenotypes.

Neither a pureed diet nor analgesics were required. Using the Radiation Therapy Oncology Group scoring system, those symptoms quantify as grade 1 acute radiation morbidity of the pharynx, esophagus, and larynx. No acute toxicity to the skin was observed.

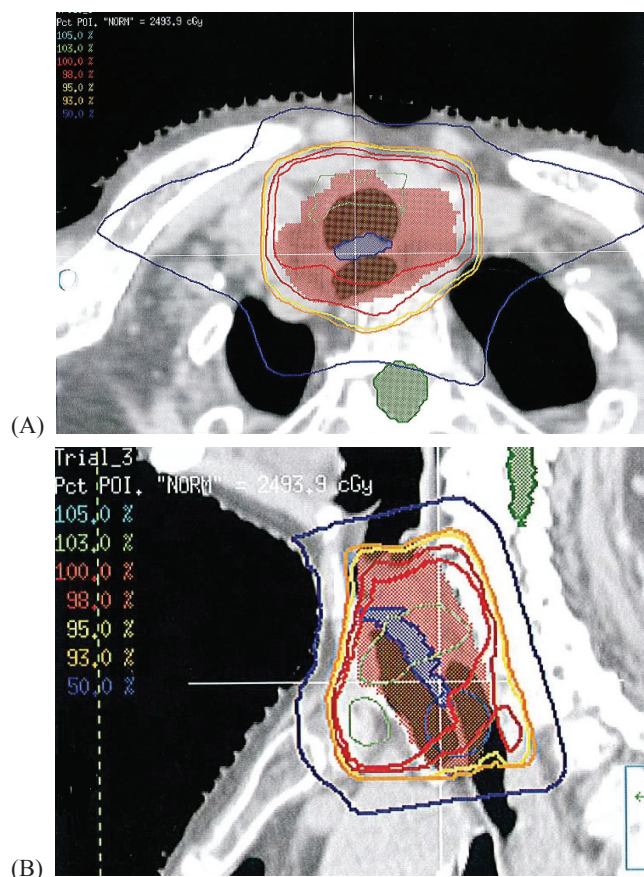


FIGURE 3 Three-dimensional conformal radiotherapy plans in the (A) axial and (B) sagittal views. Gross tumour volume boost delivered to the blue-shaded area in the isodose curves.

Fibre-optic examination 1 week after treatment revealed mild erythema of the laryngeal mucosa and thickened secretions, with complete resolution of the patient's airway symptoms.

The radiotherapy was successful in putting the extranodal RDD into long-term remission. One year post radiotherapy, the patient underwent head-and-neck computed tomography that was negative for lesions at the sites previously affected by the subglottic RDD (Figure 4). Follow-up continued for 2 years without any clinical or radiologic findings suggestive of local recurrence.

3. DISCUSSION

Rosai and Dorfman first described 4 cases of the clinicopathologic entity known as sinus histiocytosis with massive lymphadenopathy in 1969^{1,2}. This benign disorder usually affects young adults and children, with no predilection by sex. Presentation with large bilateral painless cervical lymphadenopathy, with or without fever, is the hallmark of this condition, occurring in 89% of cases^{1,2}. Extranodal involvement occurs in fewer than half of cases and is more common in elderly patients³. Skin, nasal cavity or paranasal sinuses, soft

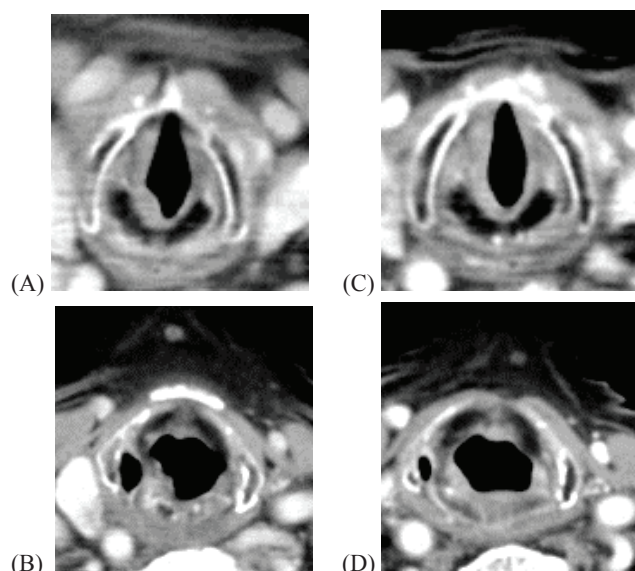


FIGURE 4 Computed tomography scans of the head and neck in the axial plane showing right-sided Rosai-Dorfman lesion of the subglottis (A,B) before and (C,D) after radiation therapy.

tissue, orbit, and bone are the most frequently seen sites of extranodal RDD⁴. Lymphadenopathy usually accompanies extranodal RDD; however, isolated extranodal presentations of this entity in various head-and-neck anatomic sites have been described⁵.

Important in the diagnosis of RDD is the demonstration, upon pathology examination, of emperipolesis of leukocytes and concurrent histiocytosis¹. Histiocytes in RDD lesions have abundant cytoplasm. As well, molecular features have been noted in RDD lesions; immunohistochemistry reveals the presence of CD1a, CD68, CD163, α_1 -antichymotrypsin and S-100^{6,7}.

No ideal treatment protocol exists for the management of RDD. Initial management usually consists of either incisional or excisional biopsy, followed by observation in most cases. Further surgical management is usually reserved for recurrent lesions causing functional disability or obstruction of critical structures. Corticosteroids are frequently used, with approximately one third of patients achieving a complete (CR) or partial (PR) response to treatment⁷. Chemotherapy (single agents and combinations) has been used with limited success. Various classes of chemotherapeutic agents have been used, including alkylating agents, antimetabolites, and vinca alkaloids.

Extranodal RDD of the larynx has been documented in the literature⁸⁻¹⁸. In these cases, treatment was initiated because of symptoms such as stridor, dysphagia, dysphonia, and dyspnea because of a laryngeal lesion. Subglottic RDD was treated by radiation therapy in only 1 of the cases, with no evidence of disease recurrence at 16 months' follow-up¹⁰.

In 1990, 418 cases of RDD were reviewed by Komp⁸. Radiotherapy treatment was documented in 34 patients, but the radiation dose was reported in only 18. In 5

patients who received an intermediate lymphoma-type dose between 30 Gy and 49 Gy, 1 patient had a CR, 1 patient had a PR, and 3 patients had no response (NR). Radical doses (>50 Gy) were used in 2 patients, achieving 1 PR and 1 NR. The remaining 11 patients received doses of less than 30 Gy, achieving 3 PRs and 8 NRS.

The controversy about whether a radiation dose–response relationship exists for RDD lesions cannot currently be resolved for several reasons, including missing treatment data, poor reporting of radiation cases, infrequent use of radical radiation doses, and the rarity of this disease entity. In a review of the recent literature since the publication of the Komp review, we identified 4 cases of RDD lesions that responded to radiation (Table 1)^{20–23}. Although

those cases do not assist with the issue of the proper dose–fractionation schedule for RDD lesions, they do provide some evidence that, in selected cases, disease recurrence can be prevented or delayed with the use of either primary or postoperative radiotherapy.

4. CONCLUSIONS

A steroid-resistant subglottic RDD lesion causing respiratory distress responded well to external-beam radiotherapy, with durable symptom control. A multidisciplinary approach to the management of primary and recurrent RDD lesions is required to provide good local control and functional results for individual patients. Reporting of future cases treated

TABLE 1 Literature review of Rosai–Dorfman disease treated with radiation therapy since 1990

Reference	Tumour site	Presentation	Radiation therapy	Clinical course
Petzold <i>et al.</i> , 2001 ²⁰	Brain	Male, 47 years old Multiple brain metastases on MRI Suprasellar mass resected	External-beam radiotherapy, 20 Gy in 10 fractions, technique unknown	Improved vision and motor examination Reduction of sellar mass on 1-year follow-up MRI
Childs and Kim, 1999 ²¹	Bilateral orbits	Male, 28 years old Bilateral orbital and periorbital disease and enlarged cervical lymph node Progression on steroids, and no response to vincristine	External-beam radiotherapy 20 Gy in unknown number of fractions, 5-field lens-sparing technique with 2 photon and 3 electron beams; complete response after completion of radiation	Recurrence in left eye at 6 years; minimal response to steroids, complete response to resection Recurrence in right eye at 11 years; 2 resections with regrowth of tumour; external-beam radiotherapy with 18 Gy in 10 fractions, wedge pair to right eye, no toxicity, minimal response
Kelly <i>et al.</i> , 1999 ²²	Pituitary gland	Female, 45 years old Pituitary tumour (2 cm) with suprasellar extension on MRI Transsphenoidal resection of tumour	Unknown dose and toxicity of radiation treatment post resection; no evidence of disease at 4 years of follow-up	T2 cord compression MRI at 12 months, treated with surgical decompression and postoperative external-beam radiotherapy, unknown dose and toxicity; no evidence of disease at 3 years. Sphenoid sinus tumour at 21 months, treated with external-beam radiotherapy, unknown dose and toxicity; no evidence of disease at 2 years
Annessi and Giannetti, 1996 ²³	Skin	Female, 38 years old Multiple leg, nose, and back papules	Back nodules treated with external-beam radiotherapy, 45 kV photons, 14 Gy in 7 fractions given weekly; leg lesions treated with external-beam radiotherapy, 150 kV photons 40 Gy in 40 fractions; no observed toxicity, all lesions showed complete response at 3 months	No evidence of disease at 3 years

MRI = magnetic resonance imaging.

with radiotherapy should include detailed descriptions of treatment dose, fractionation, technique, toxicity, and outcome to provide clinicians with reliable data on which to base future treatment decisions.

5. CONFLICT OF INTEREST DISCLOSURES

The authors have no conflicts of interest, sources of financial support, corporate involvement, or patent holdings to declare for the present work.

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Correspondence to: Varagur Venkatesan, London Regional Cancer Centre, Department of Radiation Oncology, 790 Commissioners Road East, London, Ontario N6A 4L6.

E-mail: Varagur.Venkatesan@lhsc.on.ca

* University of Western Ontario, Schulich School of Medicine and Dentistry, London, ON.

† London Regional Cancer Program, Department of Radiation Oncology, London, ON.

‡ London Health Sciences Centre, Department of Pathology, London, ON.

§ London Health Sciences Centre, Department of Otolaryngology—Head and Neck Surgery, London, ON.