Radiotherapy for steroid-resistant laryngeal Rosai–Dorfman disease

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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.
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.

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

**Figure 2** Histology micrographs demonstrating classical features of Rosai–Dorfman disease: (A) histiocytosis, expanded paracortex, and reduced number of follicles with germinal centers; (B) emperipolosis; (C) positive staining for the CD68, CD163, and S-100 immunophenotypes.
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 patients.3 Skin, nasal cavity or paranasal sinuses, soft tissue, orbit, and bone are the most frequently seen sites of extranodal RDD.4 Lymphadenopathy usually accompanies extranodal RDD; however, isolated extranodal presentations of this entity in various head-and-neck anatomic sites have been described.5

Important in the diagnosis of RDD is the demonstration, upon pathology examination, of emperipolesis of leukocytes and concurrent histiocytosis.1 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, α1-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 treatment.7 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 literature.8–18 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-up.10

In 1990, 418 cases of RDD were reviewed by Komp.8 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 NRSs.

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

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<td>Multiple leg, nose, and back papules</td>
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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.

6. REFERENCES


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