Upfront radiotherapy for diffuse lymphangiomatosis in a child

Abhishek Purkayastha, Neelam Sharma, Shuvendu Roy¹, Chetan Agarwal²

Departments of Radiation Oncology, ¹Pediatrics and ²Pathology and Molecular Sciences, Army Hospital Research and Referral, New Delhi, India

ABSTRACT

Lymphangiomatosis is an extremely rare multisystem disorder resulting from congenital malformations of lymphatic development mainly affecting the pulmonary and skeletal systems without a preset therapeutic approach. We hereby present a unique case of diffuse lymphangiomatosis in a 2-year-old male child who presented with massive right pleural effusion, ascites, right hydrocele, and lytic lesions in right hemipelvis, vertebrae, and femur. Biopsy from right thigh revealed lymphangiomatosis. The child was treated with upfront conformal radiotherapy (RT) to the affected sites with fractionated doses of 18–20 Gy which he tolerated well. Post-therapy evaluation by imaging showed a significant response to radiation with excellent symptomatic relief. Presently, he is on follow-up for over 1 year with a Karnofsky performance status of 90% without any evidence of progression of the disease. The aim of reporting this case is to sensitize the medical fraternity about RT as an effective, noninvasive, definitive therapeutic modality for treating this uncommon disease.

Key words: Benign disease, child, diffuse lymphangiomatosis, radiotherapy

INTRODUCTION

Lymphangiomatosis is a benign disorder of congenital malformations of lymphatic development occurring before the 20th week of gestation.¹ It is characterized by the presence of proliferative differentiated lymphatic tissues called lymphangiomas¹ infiltrating adjacent organs mainly the pulmonary and skeletal systems, with poor prognosis in children as compared to adults.¹² Due to its rarity, wide spectrum of clinical features, and a lack of randomized clinical trials apart from a few case reports, it has been difficult to diagnose and establish a definitive treatment protocol. We report this case to highlight its rare unilateral, multi-organ involvement and the role of radiotherapy (RT) in the treatment of this condition.

CASE REPORT

A 2-year-old male child presented with progressive dyspnea, chest pain, abdominal distension, hydrocele, and right lower limb swelling since 4 months [Figure 1]. He was averagely nourished though taking less feeds due to increasing symptoms. His hematological, lipid and biochemical profiles including albumin levels were normal. Chest and abdominal radiograph showed

Address for correspondence: Dr. Abhishek Purkayastha, Department of Radiation Oncology, Army Hospital Research and Referral, Dhaula Kuan, Delhi Cantonment - 110 010, Delhi, India. E-mail: abhi5296@gmail.com
massive right pleural effusion causing collapse of the right lung with contralateral mediastinal shift and ascites [Figure 2]. Computed tomography (CT) scan of chest, abdomen and pelvis showed gross right pleural effusion, moderate ascites, hydrocele, lytic lesions involving right ilium, ala of sacrum [Figure 3], ischium, pubic bone, shaft of the right femur, and D-12 to S-2 vertebrae. Angiography of lower limbs showed no arteriovenous malformation. Pleural tapping showed chylous effusion leading to drainage of 1–1.5 L fluid per day. Image-guided trucut biopsy of pleural peel and lung tissue showed chronic inflammation and was negative for malignancy.

Magnetic resonance imaging (MRI) of lower limbs [Figure 4] showed the involvement of soft tissue and muscles of the right hip, thigh, knee, and right hemiscrotum with lymphatic changes within. Trucut biopsy from right thigh showed closely packed small vascular channels lined by flattened endothelial cells favoring lymphangiomatosis [Figure 5]. Immunohistochemistry (IHC) stained positive for CD 34 [Figure 6] and D2-40. Since the child was highly symptomatic and not responding to pleural fluid drainage and dietary modifications, he was treated with conformal RT to right hemithorax to a dose of 18 Gy in 12 fractions, right hemipelvis, and right thigh to a dose of 20 Gy in 11 fractions. He tolerated treatment well and showed an excellent symptomatic response to therapy with a significant reduction in his dyspneic episodes, chest and body pain. Presently, the patient is on close follow-up of over 1 year with a Karnofsky performance status of 90%, and his latest radiograph chest and abdomen showed significant radiological improvement [Figure 7].

**DISCUSSION**

Lymphangiomatosis describes an extremely uncommon, benign congenital disorder of the lymphatic system.
where lymphatic channels increase in number and size and gets interconnected in an aberrant or haphazard fashion resulting in the formation of dilated sacs or cysts known as lymphangiomas[1] which invade surrounding organs or structures causing morbid conditions for the affected individual by compression or mass effect, restrictive, or obstructive mechanisms[1] by virtue of proliferation, thickening, dilatation leading to leakage causing accumulation of fluid which puts pressure on the vital organs, thus making them incapable to function properly.

The disorder has no sex predilection or familial pattern, presents in both infants and adults but is more aggressive in children with poor prognosis[1,2] with 40% mortality as compared to adults.[3] The primary cause of death in children is an accumulation of chylous fluid composed of lymph and fats in the pleural and pericardial space causing mass effect, respiratory failure, and superadded infections. Although the exact cause of lymphangiomatosis is still unknown, the presence of vascular endothelial growth factor receptor-3 (VEGFR-3) responsible for the growth of lymphatics in high amounts in affected tissues may be a possible cause.[2]

Lymphangiomatosis is a unique multi-organ disorder affecting mainly the pulmonary and skeletal system except central nervous system.[4] Our case showed a peculiar disseminated pattern with the involvement of the right lung, peritoneum, right hemiscrotum, right lower limb muscles and bones. It may initially present with vague symptoms like a cough or wheeze, resulting in under-diagnosis with patients eventually presenting in an advanced stage with life-threatening complications such as severe cough, hemoptysis, dyspnea, chest pain, and tachycardia. Abdominal involvement manifests as pain, distension, vomiting, diarrhea, or hematuria if kidneys are affected. Bone affection presents as limb swelling, bone pain, pathological fracture, and paraplegia on spinal involvement.

Diagnosing lymphangiomatosis may be challenging due to its rarity, varied clinical, and imaging presentation. It may mimic other pathologies such as Gorham’s disease, Hajdu-Cheney disease, lymphangioleiomyomatosis lymphangiectasis, pulmonary hemangiomatosis, Kaposi’s sarcoma, kaposiform hemangioendothelioma, obstructive lung diseases, respiratory infections, congenital or secondary hydrocele, hypertrophic myopathies, or hepatobiliary pathology. History and physical examination, chest radiographs, pulmonary function tests, ultrasonography, CT scans, MRI, and lymphoscintigraphy are required to determine the location and extent of the disease. Diagnosis is established by histological examination of affected tissues[4] characterized by benign-appearing lymphatic
vessels and IHC positive for factor VIII-related antigen, pulmonary endothelial markers CD 31, CD 34, and lymphatic endothelial marker D2-40 which stains lymphatic channel endothelium but not the adjacent blood vessel.

Treatment of lymphangiomatosis has been predominantly symptomatic. Procedures such as thoracentesis, pericardiocentesis, pleuropertoneal shunt, sclerotherapy, and bone grafts have been used. Drugs such as thalidomide, steroids, propranolol, sirolimus, interferon alpha-2b, bisphosphonates, and VEGFR-3 inhibitor bevacizumab are used apart from total parenteral nutrition and high protein diet. Khunte et al. used glucocorticoids, while we used RT that has been used in patients with pulmonary, abdominal, muscular, and cutaneous involvement with excellent results. Some oncologists have used 40 Gy for pelvic and 26 Gy for abdominal while 20 Gy or 18 Gy for pulmonary lymphangiomatosis to prevent any radiation pneumonitis or lung fibrosis. The exact mechanism of response to radiation is not known, but it possibly results in lymphatic endothelial edema and fibrosis leading to obstruction of the abnormal lymphatic channels.

Most available information about diffuse lymphangiomatosis is based on sporadic case reports. This entity should always be considered in patients with lytic bone lesions accompanied by chylous effusions, especially in pediatric patients presenting with symptoms and signs of interstitial lung disease, to enable a prompt initiation of appropriate management. Emphasis should be given to treatment trials to determine long-term efficacy and safety of therapeutic modalities. We hereby recommend radiation therapy as one of the effective, noninvasive and nontoxic treatment modality.

Acknowledgments
We would like to thank the father of the patient for permitting us to publish the case report and use the clinical images.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Faul JL, Berry GJ, Colby TV, Ruoss SJ, Walter MB, Rosen GD, et al. Thoracic lymphangiomas, lymphangiectasis, lymphangiomatosis, and lymphatic dysplasia syndrome. Am J Respir Crit Care Med 2000;161:1037-46.
2. Tran D, Fallat ME, Buchino JJ. Lymphangiomatosis: A case report. South Med J 2005;98:669-71.
3. Alvarez OA, Kjellin I, Zuppan CW. Thoracic lymphangiomatosis in a child. J Pediatr Hematol Oncol 2004;26:136-41.
4. Chander B, Dogra SS, Kaul R, Preet K, Sharma R, Chauhan NS. Lymphangiomatosis: Two cases with unique presentations, salience of nomenclature, and diagnosis. J Cancer Res Ther 2015;11:652.
5. Du MH, Ye RJ, Sun KK, Li JF, Shen DH, Wang J, et al. Diffuse pulmonary lymphangiomatosis: A case report with literature review. Chin Med J (Engl) 2011;124:797-800.
6. Khunte P, Beck P, Khunte S, Prakash D. A rare case of pulmonary lymphangiomatosis from the tribal zone of central India. Int J Res Med Sci 2015;3:2495-8.
7. Rostom AY. Treatment of thoracic lymphangiomatosis. Arch Dis Child 2000;83:138-9.
8. Johnson DW, Klazynski PT, Gordon WH, Russell DA. Mediastinal lymphangioma and chylothorax: The role of radiotherapy. Ann Thorac Surg 1986;41:325-8.
9. Dajee H, Woodhouse R. Lymphangiomatosis of the mediastinum with chylothorax and chylopericardium: Role of radiation treatment. J Thorac Cardiovasc Surg 1994;108:594-5.
10. Kandil A, Rostom AY, Mourad WA, Khafaga Y, Gershuny AR, el-Hosseiny G. Successful control of extensive thoracic lymphangiomatosis by irradiation. Clin Oncol (R Coll Radiol) 1997;9:407-11.