Long-term Effects of Epoprostenol on the Pulmonary Vasculature in Idiopathic Pulmonary Arterial Hypertension

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The current treatment of pulmonary arterial hypertension (PAH) uses vasodilator drugs. Although they improve symptoms associated with PAH, their chronic effects on the pulmonary vasculature and the right ventricle (RV) in humans remain unknown. We report the autopsy findings from a patient with idiopathic PAH treated with epoprostenol successfully for 18 years. The patient died of colon cancer. The pulmonary vasculature surprisingly showed extensive changes of a proliferative vasculopathy. Immunohistochemical studies confirmed ongoing cellular proliferation. Studies of the RV demonstrated concentric hypertrophy with seemingly preserved contractility. The myocardium shifted to glycolytic metabolism. Although the long-term use of epoprostenol contributed to the patient's increased survival, it did not prevent progression of the underlying vascular disease. Remarkably, the RV was able to sustain a normal cardiac output in the face of advanced vascular pathology. The mechanisms by which the RV adapts to chronic PAH need further study. *CHEST* 2010; 138(5):1234-1239

Abbreviations: DAPI = 4',6-diamidino-2-phenylindole; Glut1 = glucose transporter; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PDK4 = pyruvate dehydrogenase kinase-4; PNCA = proliferating cell nuclear antigen; RV = right ventricle; SERCA2A = sarcoplasmic reticulum calcium adenosine triphosphatase

There are three classes of approved therapies for pulmonary arterial hypertension (PAH): endothelin receptor blockers, phosphodiesterase-5 inhibitors, and prostacy-

clins. Although all are pulmonary vasodilators, they have other properties beyond pulmonary vasodilation that could be beneficial in PAH. Of the three classes, the prostacyclins are considered the most effective and often are initiated in patients who have failed all other therapies.¹

Presently, it remains speculative how these drugs act on the pulmonary vasculature in PAH. Although it is presumed that they have the potential to reverse vascular remodeling based on animal models of PAH,² there never has been histologic confirmation of this in humans. We report on the lung pathology of a patient with idiopathic PAH (IPAH) who was on IV epoprostenol for 18 years and did well without developing right-sided heart failure or needing hospitalization for pulmonary hypertension. The patient died of metastatic colon cancer. A postmortem examination was performed. We were interested in whether the pulmonary vasculature would have a relatively normal appearance that suggested disease reversal or whether there would be pathologic lesions of PAH. In addition, we were interested in studying the right ventricle (RV) to better understand how it had adapted to the PAH so remarkably well.

CASE REPORT

The patient was a 53-year-old woman who presented with unexplained dyspnea at age 31 in 1987. A thorough evaluation revealed IPAH as the etiology. She had an elevated pulmonary arterial pressure and pulmonary vascular resistance at cardiac catheterization (Table 1) but was found to be nonvasoreactive to vasodilator challenge and was managed conservatively. In 1991, the patient entered the pivotal clinical trial of epoprostenol for IPAH³ and was randomized to active therapy, which she remained on from that time onward. Her initial response was a reduction in dyspnea and improvement in functional class, characteristic of the efficacy of epoprostenol in PAH.⁴ She was maintained on a dose of 60 ng/kg/min and lived an active life with mild symptoms (World Health Organization functional class 2). Serial cardiac catheterizations (Table 1) and exercise tests confirmed the stable state of her IPAH. At her last treadmill test in 2007, the patient walked for 13 min on a Naughton-Balke protocol (equivalent to 7.6 metabolic equivalent tasks)⁵

In July 2009, the patient presented with malaise and abdominal pain attributed to a common bile duct gallstone.

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In the course of her evaluation, she was noted to be quite cachectic with a palpable supraclavicular lymph node. Further evaluation revealed metastatic adenocarcinoma of the colon. She was started on chemotherapy (5-fluorouracil and irinotecan) but had a continuous decline in health and could not tolerate the treatments. She died 3 weeks later. A postmortem examination was performed.

Histologic Evaluation of the Pulmonary Vasculature and RV

The lungs were perfused with formalin prior to sectioning. Hematoxylin and eosin staining and immunohistochemistry were performed on formalin-fixed, paraffin-embedded tissue using standard techniques. Immunostaining for assessment of inflammation and thrombosis in the pulmonary vasculature was performed on the automated Bond TM system (Leica Microsystems; Bannockburn, IL) using the following antibodies: anti-CD20 (clone L26), anti-CD8 (clone 8/144B), anti-CD68 (clone PG-M1), and anti-CD4 (clone CD4-368) (DakoCytomation; Carpinteria, CA). The immunostaining was performed according to modified manufacturer protocol following antigen retrieval with ER1 for CD20 (30 min) and ER2 for CD4, CD8, and CD68 (20 min). Immunofluorescence for assessment of vascular proliferation and RV metabolism was done after antigen retrieval (95–100°C for 30 min in citrate buffer) with the following primary antibodies (Abcam; Cambridge, MA) incubated overnight at 4°C: proliferating cell nuclear antigen (PCNA) (1:500), sarcoplasmic reticulum calcium adenosine triphosphatase (SERCA2A) (1:200) (Bethyl Laboratories; Montgomery, TX), dystrophin (1:100), smooth muscle actin (1:300), glucose transporter (Glut1) (1:200), and pyruvate dehydrogenase kinase-4 (PDK4) (1:40). Slides subsequently were incubated with secondary antibodies (Alexa Fluor 488 [1:400] and Alexa Fluor 568 [1:400]; Invitrogen; Carlsbad, CA) for 1 h at 25°C. The antifade reagent (Prolong Gold; Invitrogen) contained 4',6-diamidino-2-phenylindole (DAPI) to stain the nuclei of the cells. Images were acquired with the Zeiss LSM 510 META confocal microscope (Carl Zeiss AG; Oberkochen, Germany) using the 488 nm and 561 nm lasers. The DAPI was visualized with the Chameleon Ultra 2 photon laser (Coherent Inc; Santa Clara, CA) at 770 nm.

RESULTS

Histopathologic Findings of the Pulmonary Circulation

The small- to medium-sized pulmonary arteries demonstrated severe muscular hypertrophy and intimal fibrosis with occasional complete occlusion of the lumen. There were frequent plexiform lesions adjacent to arterial branch points, most of which had associated vascular dilatation (Fig 1). Immunostaining revealed the presence of occasional small platelet thrombi and a mild inflammatory infiltrate in the plexiform lesions consisting of CD4⁺ and CD8⁺ T cells, CD68⁺ macrophages, and rare CD20⁺ B cells, as previously reported⁶ (results not shown). Additionally, there was prominent staining for PCNA in the

endothelium and media of the medium-sized pulmonary arteries, in the inflammatory cells in the adventitia, and in the plexiform lesions (Fig 1), indicating that cellular proliferation was present.⁷

Gross and Histopathologic Findings of the RV

The total weight of the heart was 302 g, which is within normal limits. The RV had severe concentric hypertrophy with a wall thickness of 1.0 cm, but it did not have the characteristic dilatation and interventricular septal distortion that is typically seen in chronic PAH (Fig 2).⁸ On histologic examination, severe myocyte hypertrophy was present in the RV. For comparison, we also performed similar studies on the heart from a patient with IPAH who was treated with epoprostenol but died of RV failure.

Immunostaining revealed expression of SERCA2A in both ventricles at levels similar to a normal patient, whereas the patient who died of RV failure had less SERCA2A expression in her RV than in her left ventricle (Fig 2). To gain insight into the state of myocardial metabolism in our patient, we examined a variety of glycolytic markers and found an increase in the expression of both Glut1 and PDK4 in the RV relative to control, which is consistent with the presence of a glycolytic metabolic state; however, this appeared to be at a more modest level than what was observed in the patient with RV failure.

DISCUSSION

There are several treatments approved specifically for PAH.¹ Although all are vasodilators, each class of treatment has been demonstrated to have some degree of antiproliferative effect on vascular smooth muscle cells either in vitro or in animal models of PAH.^{9–11} Although clinical trials have demonstrated that they have only modest effects on lowering the pulmonary arterial pressure, it has been proposed that the long-term use of these therapies may reverse some of the pulmonary vascular remodeling that occurs with PAH, thus providing an explanation for the delayed time to clinical worsening and improved long-term survival that has been reported.¹² For ethical reasons, it has not been possible to perform serial open-lung biopsies to evaluate directly the effect these drugs may have on the pulmonary vasculature in humans. In addition, the effects that these treatments have on RV function have not been well characterized.

The patient in this report had a successful response to epoprostenol therapy, as she lived for 18 years without ever developing a decline in exercise tolerance or right-sided heart failure. Her initial hemodynamic response to epoprostenol was maintained throughout her life. It is notable that her pulmonary arterial pressures never returned to normal, but the pathology study reported from the National Heart, Lung, and Blood Institute Primary Pulmonary Hypertension Registry¹³ found no correlation between the severity of the pulmonary vascular lesions on autopsy and the level of the pulmonary arterial pressures. Thus, the status of her pulmonary vasculature remained an open question.

The extensive pulmonary vascular disease in this patient, despite 18 years of effective treatment, is surprising and

Table 1—Hemodynamics of Patient Before and During Treatment With Epoprostenol

Date	Drug	RA, mm Hg	PAP (mm Hg)	CO, L/min	PVR, units
July 1987	None	3	74/30 (43)	6.24	6.40
November 1991	None	8	128/54 (72)	3.40	16.7
February 1992	Epoprostenol	5	97/34 (51)	6.64	9.20
March 1998	Epoprostenol	6	90/39 (47)	6.10	6.90
February 2005	Epoprostenol	7	95/54 (63)	7.60	7.84

CO = cardiac output; PAP = pulmonary arterial mean pressure; PVR = pulmonary vascular resistance; RA = right atrial pressure.

provides instructive lessons for the current and future treatment of PAH. Although the pathologic changes in her pulmonary vasculature were unknown at the time the epoprostenol was initiated, it is unrealistic to believe that they were more advanced than at the time of her death, suggesting that the epoprostenol did not reverse her vascular disease and likely allowed it to progress. Indeed, we demonstrated the presence of vascular proliferation, which was confirmed by the PCNA staining (Fig 1).⁷ Thus, despite the fact that prostanoids have the potential to inhibit vascular smooth muscle growth *in vitro*,⁹ this case suggests that they may not have a significant effect directly on the pulmonary vasculature in IPAH beyond pulmonary vasodilation.

The mechanisms of action of pulmonary vasodilators in PAH remain uncertain because none of the therapies restore normal hemodynamics.¹⁴ A pathology study of PAH in congenital heart disease¹⁵ and two case reports in IPAH^{16,17} suggested that for reversal of the pulmonary vascular remodeling to occur, a substantial reduction in pulmonary arterial

pressure is essential. Unfortunately, with the exception of vasoreactive patients treated with calcium channel blockers,¹⁸ this magnitude of reduction is rare with existing PAH therapies. In the case of IV epoprostenol, its predominant hemodynamic effect in PAH is to increase the cardiac output because the dose can be titrated upward until the cardiac output becomes normal in most patients.¹⁹ It appears from this case that the effect on cardiac output may explain why epoprostenol sustains patients with PAH over time and why it is more effective than the other vasodilators.

This case also illustrates that excellent survival in PAH is possible despite an advanced proliferative vasculopathy and points to the importance of preserved RV function as a determinant of survival. Studies repeatedly have shown that survival in PAH is related to RV function.²⁰ Why the RV did not fail in this patient is intriguing. The fact that the RV had concentric hypertrophy rather than severe dilation may be one reason.²¹ The development of concentric vs eccentric ventricular hypertrophy is governed by many factors, including genetics.²² Thus, it remains unknown whether the response in this patient was genetically determined or whether the initiation of epoprostenol before severe RV dilation occurred was a key factor. These important questions need further study. It was also remarkable that there was seemingly normal SERCA2A expression in the RV, reflecting reasonable preservation of RV contractility.²³ It is possible that epoprostenol exerts its beneficial effects on the RV by increasing cyclic adenosine monophosphate, a known inotropic mediator.²⁴

The important mechanisms behind chronic RV adaptation to PAH are not well understood, but studies have shown that the myocardium in hypertrophied states undergoes a glycolytic metabolic shift,²⁵ as was demonstrated in this patient by the upregulation of PDK4 and Glut1. There is debate about whether this response is adaptive or maladaptive.²⁶ Recent animal data support the concept that upregulated Glut1 and PDK4 are associated with increased glycolysis and impaired oxygen-consumption in RV hypertrophy.²⁷ The increased Glut1 may reflect the need to increase glucose import to compensate for the reduced adenosine triphosphate yield in glycolytic vs oxidative metabolism.²⁷ One human study in IPAH reported an increased RV uptake of fluorodeoxyglucose with PET scan consistent with a glycolytic state, which was partially reversed in patients who responded to epoprostenol therapy.²⁸ A better understanding of the adaptive mechanisms that allow the RV to sustain an increased workload over time appears to be critically important.

Because this is a single case report, one needs to be cautious about extrapolating these findings to all patients

FIGURE 1. A, A small branch of pulmonary artery with severe medial hypertrophy and mild intimal fibrosis causing severe luminal obstruction (hematoxylin-eosin stain, original magnification $\times 20$). These findings were typical of most of the arterioles in this patient. B, A characteristic plexiform lesion surrounded by dilated, thin-walled vessels (hematoxylin-eosin stain, original magnification $\times 4$). C, Immunofluorescent staining for proliferating cell nuclear antigen (PCNA) (red) indicative of ongoing cellular proliferation. The bright staining (green) is smooth muscle actin. The staining of the pulmonary vasculature from another patient who died without pulmonary vascular disease is shown for comparison as a normal control. Staining for PCNA is absent in the normal control. PAH = pulmonary arterial hypertension.

FIGURE 2. A, The heart of our patient with PAH (in cross section) showing severe concentric RV hypertrophy is presented adjacent to a patient with idiopathic PAH (IPAH) who died of severe RV failure for comparison. There is a striking difference in the geometry of the RV in these patients. B, Representative immunofluorescent staining of the RV and left ventricle (LV) myocardium for SERCA2A in our patient is shown alongside a sample from the patient who died of severe RV failure and a normal control. The mean fluorescent intensity, normalized to dystrophin, also is displayed (right). The intensity in the RV and LV appear to be similar between the long-term surviving patient and the normal control but diminished in the RV when compared with the LV in the patient who died of RV failure. C, PDK4 (green) and Glut1 expression are shown in our patient with PAH alongside the patient who died of severe RV failure and the normal control. There is increased expression of PDK4 and Glut1 in our patient's RV compared with her LV and compared with the normal control. However, there appears to be less upregulation when compared with the patient who died of severe RV failure. In all RV micrographs, the bar indicates 100 μ m. DAPI = 4',6-diamidino-2-phenylindole; Glut1 = glucose transporter; PDK4 = pyruvate dehydrogenase kinase-4; RV = right ventricle; SERCA2A = sarcoplasmic reticulum calcium adenosine triphosphatase. See Figure 1 legend for expansion of other abbreviation.

with IPAH. It remains unknown whether other classes of vasodilators have any antiproliferative effects in human PAH and how they affect RV contractility in patients with persistently elevated pulmonary artery pressure. The

glycolytic metabolism in the RV of this patient needs further study to know whether it is characteristic of the RV in PAH and whether it represents an important adaptive or maladaptive response. In addition, it is unknown whether the

coexistence of advanced cancer had any influence. However, given the uncommon incidence of IPAH and our inability to sample the pulmonary vasculature serially in humans, we need to learn as much from these cases as possible.

In conclusion, we have demonstrated that a patient with IPAH can respond to epoprostenol for an extended period while the underlying pulmonary vascular disease continues to progress. In addition, we have shown that it remains possible for RV function to adapt to advanced PAH and maintain relatively normal function. The lessons from this case hopefully will stimulate new directions in the therapeutic strategies for PAH that focus on improving RV function, even in the presence of advanced pulmonary vascular disease. Additionally, novel therapies directed at reversing the remodeling of the pulmonary vasculature rather than vasodilation are sorely needed because it appears that the actual reversal of PAH remains a daunting challenge.

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REFERENCES

1. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med*. 2004;351(14):1425-1436.
2. Cowan KN, Heilbut A, Humpl T, Lam C, Ito S, Rabinovitch M. Complete reversal of fatal pulmonary hypertension in rats by a serine elastase inhibitor. *Nat Med*. 2000;6(6):698-702.
3. Barst RJ, Rubin LJ, Long WA, et al; The Primary Pulmonary Hypertension Study Group. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med*. 1996;334(5):296-302.
4. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation*. 2002;106(12):1477-1482.
5. Shah SJ, Thenappan T, Sur J, Rich S, Archer SL, Gombert-Maitland M. Value of exercise treadmill testing in the risk stratification of patients with pulmonary hypertension. *Circ Heart Fail*. 2009;2(4):278-286.
6. Tuder RM, Groves B, Badesch DB, Voelkel NF. Exuberant endothelial cell growth and elements of inflammation are present in plexiform lesions of pulmonary hypertension. *Am J Pathol*. 1994;144(2):275-285.
7. Naryzhny SN. Proliferating cell nuclear antigen: a proteomics view. *Cell Mol Life Sci*. 2008;65(23):3789-3808.
8. Louie EK, Rich S, Levitsky S, Brundage BH. Doppler echocardiographic demonstration of the differential effects of right ventricular pressure and volume overload on left ventricular geometry and filling. *J Am Coll Cardiol*. 1992;19(1):84-90.

9. Clapp LH, Finney P, Turcato S, Tran S, Rubin LJ, Tinker A. Differential effects of stable prostacyclin analogs on smooth muscle proliferation and cyclic AMP generation in human pulmonary artery. *Am J Respir Cell Mol Biol*. 2002;26(2):194-201.
10. Yang Z, Krasnici N, Lüscher TF. Endothelin-1 potentiates human smooth muscle cell growth to PDGF: effects of ETA and ETB receptor blockade. *Circulation*. 1999;100(1):5-8.
11. Wharton J, Strange JW, Møller GM, et al. Antiproliferative effects of phosphodiesterase type 5 inhibition in human pulmonary artery cells. *Am J Respir Crit Care Med*. 2005;172(1):105-113.
12. Galie N, Manes A, Negro L, Palazzini M, Bacchi-Reggiani ML, Branzi A. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. *Eur Heart J*. 2009;30(4):394-403.
13. Pietra GG, Edwards WD, Kay JM, et al. Histopathology of primary pulmonary hypertension. A qualitative and quantitative study of pulmonary blood vessels from 58 patients in the National Heart, Lung, and Blood Institute, Primary Pulmonary Hypertension Registry. *Circulation*. 1989;80(5):1198-1206.
14. Rich S. The current treatment of pulmonary arterial hypertension: time to redefine success. *Chest*. 2006;130(4):1198-1202.
15. Wagenvoort CA, Wagenvoort N, Draulans-Noë Y. Reversibility of plexogenic pulmonary arteriopathy following banding of the pulmonary artery. *J Thorac Cardiovasc Surg*. 1984;87(6):876-886.
16. Levy NT, Liapis H, Eisenberg PR, Botney MD, Trulock EP. Pathologic regression of primary pulmonary hypertension in left native lung following right single-lung transplantation. *J Heart Lung Transplant*. 2001;20(3):381-384.
17. Deb S, Yun J, Burton N, Omron E, Thurber J, Nathan SD. Reversal of idiopathic pulmonary arterial hypertension and allograft pneumonectomy after single lung transplantation. *Chest*. 2006;130(1):214-217.
18. Rich S, Brundage BH. High-dose calcium channel-blocking therapy for primary pulmonary hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy. *Circulation*. 1987;76(1):135-141.
19. Rich S, McLaughlin VV. The effects of chronic prostacyclin therapy on cardiac output and symptoms in primary pulmonary hypertension. *J Am Coll Cardiol*. 1999;34(4):1184-1187.
20. McLaughlin VV, Archer SL, Badesch DB, et al; ACCF/AHA, ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation*. 2009;119(16):2250-2294.
21. Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. *Circulation*. 2005;111(21):2837-2849.
22. Carabello BA. Concentric versus eccentric remodeling. *J Card Fail*. 2002;8(6 suppl):S258-S263.
23. Dillmann WH. Calcium regulatory proteins and their alteration by transgenic approaches. *Am J Cardiol*. 1999;83(12 suppl 1):89H-91H.
24. Miller OV, Aiken JW, Hemker DP, Shebuski RJ, Gorman RR. Prostacyclin stimulation of dog arterial cyclic AMP levels. *Prostaglandins*. 1979;18(6):915-925.
25. Lydell CP, Chan A, Wambolt RB, et al. Pyruvate dehydrogenase and the regulation of glucose oxidation in hypertrophied rat hearts. *Cardiovasc Res*. 2002;53(4):841-851.

26. van Bilsen M, van Nieuwenhoven FA, van der Vusse GJ. Metabolic remodelling of the failing heart: beneficial or detrimental? *Cardiovasc Res*. 2009;81(3):420-428.
27. Piao L, Fang Y-H, Cadete VJJ, et al. The inhibition of pyruvate dehydrogenase kinase improves impaired cardiac function and electrical remodeling in two models of right ventricular hypertrophy: resuscitating the hibernating right ventricle. *J Mol Med*. 2010;88(1):47-60.
28. Oikawa M, Kagaya Y, Otani H, et al. Increased [^{18}F]fluorodeoxyglucose accumulation in right ventricular free wall in patients with pulmonary hypertension and the effect of epoprostenol. *J Am Coll Cardiol*. 2005;45(11):1849-1855.

Treatment of Unicentric Castleman Disease With Neoadjuvant Rituximab

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Angiofollicular lymph node hyperplasia, known more commonly as Castleman disease, is a rare lymphoproliferative disorder. Castleman disease has two distinct clinical manifestations described as unicentric and multicentric disease. These presentations have distinct treatment algorithms and portend very different prognoses. Standard treatment of unicentric disease is complete surgical resection, which confers a cure rate approaching 100%. To our knowledge, this case report is the first to describe the use of neoadjuvant rituximab in the treatment of unicentric Castleman disease to enable a less morbid surgical resection. Given the vascularity of the tumor, proximity to the pulmonary artery and superior vena cava, and possible intimate association with the lung parenchyma, the tumor was treated preoperatively with rituximab, an anti-CD20 monoclonal antibody, at doses of 375 mg/m² weekly for 4 weeks. Rituximab therapy successfully decreased the diameter of the tumor from 4.79 cm × 2.67 cm to 2.8 cm × 1.5 cm, as confirmed by CT imaging. Postoperative surgical pathology confirmed the diagnosis of Castleman disease, hyaline vascular type, with negative margins. Notably, the lymph node tissue in the rituximab-treated specimen demonstrated reduced mantle zone thickness, decreased

size of follicles, and increased hyalinization of vessels. Rituximab shows promise in neoadjuvant treatment of unresectable or partially resectable unicentric Castleman disease. CHEST 2010; 138(5):1239-1241

Abbreviation: VATS = video-assisted thoracoscopic surgery

Angiofollicular lymph node hyperplasia, known more commonly as Castleman disease, is a rare lymphoproliferative disorder with two distinct clinical manifestations: unicentric disease and multicentric disease. These presentations have distinct treatment algorithms and portend very different prognoses. Castleman disease masses also present with three histopathologic variants—hyaline vascular, plasma cell, and mixed type—and commonly are found in the mediastinum. Standard treatment of unicentric disease is complete surgical resection, which confers a cure rate approaching 100%. Unicentric masses usually are excised with some variation of an open surgical procedure vs thoracoscopic or laparoscopic resection, with video-assisted thoracoscopic surgery (VATS) rarely used because of the highly vascular nature of the tumors. Treatment of unicentric disease also may include preoperative embolization and radiotherapy. Described here is the first documented case report of the use of neoadjuvant rituximab in the treatment of unicentric Castleman disease to allow for a less morbid surgical resection.

CASE REPORT

A 28-year-old woman presented with pleuritic chest pain. A chest radiograph demonstrated a distinct right-sided hilar lesion. CT scan confirmed a mass measuring 4.79 cm × 2.67 cm with no generalized lymphadenopathy. After a nondiagnostic bronchoscopy, the patient underwent a VATS biopsy procedure that was complicated by excessive bleeding, suggesting a highly vascular tumor. Pathology of the biopsy specimen demonstrated lymph node tissue fragments with follicles showing broad mantle zones and an onion skin pattern surrounding small germinal centers containing hyalinized vessels consistent with hyaline vascular-type Castleman disease.¹ A follow-up full-body CT scan confirmed unicentric disease.

Given the vascularity of the tumor, proximity to the pulmonary artery and superior vena cava, and possible intimate association with the lung parenchyma, it was decided to treat the mass preoperatively with the anti-CD20 monoclonal antibody rituximab at doses of 375 mg/m² weekly for 4 weeks. The patient experienced a mild infusion reaction during the first treatment that was addressed by temporarily halting the treatment, administering an antihistamine, and successfully resuming the infusion, as per protocol. No other adverse reactions occurred. The goal of neoadjuvant therapy was to reduce tumor size and vascularity to allow for a less morbid surgical resection.

Rituximab therapy successfully decreased the diameter of the tumor to 2.8 cm × 1.5 cm, as confirmed by CT scan (Figs 1, 2). The reduction in size and vascularity provided by the neoadjuvant therapy allowed for an uncomplicated resection of the mass from its hilar location, thereby avoiding the need to remove the entire right upper lobe. Postoperative surgical pathology confirmed the diagnosis of Castleman

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