

Author:

Keisuke Eguchi, M.D. and Junichi Matsui, M.D.

Affiliation:

Department of Surgery, Tokyo Dental College Ichikawa General Hospital
Address: 5-11-13 Sugano, Ichikawa, Chiba, 272-8513 Japan

TEL; +81-47-322-0151 / FAX;

+81-47-322-7931

E-mail: keguchi@tdc.ac.jp

Abstract

Pulmonary epithelioid hemangioendothelioma (PEH) is a rare pulmonary neoplasm. No reliably effective systemic chemotherapy has been established yet for this disease entity. Surgery is usually applied for patients with a small number of lesions limited to one lung, however, patients with PEH frequently present with bilateral multiple pulmonary nodules. The feasibility/efficacy/safety of surgery remains controversial for patients with bilateral multiple lung lesions. The 5-year survival probability is 60% in patients with PEH and the most frequent cause of death is pulmonary insufficiency as a result of increase in the size and/or number of tumor nodules. Presence of cases showing rapid aggravation admixed with those showing very gradual progression makes it difficult to evaluate the validity of surgery as a suitable therapeutic approach in PEH patients with multiple lung nodules. Herein, we present a summary on pulmonary epithelioid hemangioendothelioma and discuss the role of surgery in the treatment of this condition. Bilateral multiple lung tumor resections might be an acceptable therapeutic option for PEH, unless/until effective systemic therapy is established. It may be a valid therapeutic option, especially in younger patients with a longer life expectancy, if the nodules can be resected with minimal lung resection.

1. Introduction/Background

Pulmonary epithelioid hemangioendothelioma (PEH) is a rarely encountered low-grade malignant pulmonary neoplasm of endothelial origin. This unusually occurring bronchiolo-alveolar tumor with a high rate of vascular involvement was first described and labeled as intravascular bronchiolo-alveolar tumor (IVBAT) (Dail & Liebow 1975, Dail et al. 1983). It has been clarified that IVBAT is composed of cells with vascular endothelial characteristics derived from precursor mesenchymal cells (Corrin et al. 1979, Weldon-Linne et al. 1981). IVBAT is now known to be identical to epithelioid hemangioendothelioma, which is a distinctive tumor often arising from a blood vessel and characterized by epithelioid endothelial cells (Weiss et al. 1982).

2. Epidemiology

Epithelioid hemangioendothelioma (EH) can arise in various organs, including the liver, lung, soft tissue, skin, gastrointestinal tract, brain, bone, etc. The estimated prevalence of EH is less than 1 in 1,000,000 (Woodall et al. 2008). According to a registry of the International Hemangioendothelioma, Epithelioid Hemangioendothelioma, and Related Vascular Disorders (HEARD) Support Group, among 206 patients, the most commonly involved organ was the liver alone

in 21%, liver plus lung in 18%, lung alone in 12%, and bone alone in 14% of the cases (Lau et al. 2011).

The previously reported patients range in age from 7 to 83 years, with a median age at onset of 36 years (Schattenberg et al. 2008). The reported number of female patients is two- to fourfold higher than the number of male patients (Kitaichi et al. 1998, Bagan et al. 2006, Dail et al. 1983).

3. Clinical manifestations

Plain chest radiographs and computed-tomographic (CT) scans typically reveal multiple pulmonary nodules with well- or ill-defined margins and calcification. Some cases manifest solitary nodules mimicking primary lung cancer. Cavity formation is very rare. The nodules may range in size up to 2 cm, but most are less than 1 cm in diameter, and are usually located near medium-sized vessels and bronchi (Schattenberg et al. 2008). It has been reported that 18F-FDG-PET/CT is useful to evaluate the metabolic activity and search for a primary lesion and/or other metastasis in cases of PEH with multiple nodules (Rest et al. 2004, Fagen et al. 2004, Ergun et al. 2006, Watanabe et al. 2008). In most of cases, PEH is found incidentally, and the pathological diagnosis is often confirmed in surgical specimens. Immunohistochemistry for factor VIII-related

antigen, CD31 and CD34 is a useful adjunct for pathological diagnosis. Almost half of the patients with PEH are asymptomatic. Other patients mainly manifest non-specific symptoms, such as cough and/or sputum (Weiss et al. 1982), while hemorrhagic symptoms, including alveolar hemorrhage, hemoptysis, hemorrhagic pleural effusion and anemia are seen rarely (Bagan et al. 2006).

4. Treatments

Because of the rare occurrence of PEH, there are few established principles of treatment for this condition. Surgical resection is recommended in patients with a small number of lesions limited to one lung (Weiss et al. 1986, Bagan et al. 2006). In patients with a unilateral solitary nodule, wedge resection offers the same survival as anatomic resection, while the prognostic value of systematic lymph node dissection remains statistically unclear (Bagan et al. 2006). There are several case reports

published in the English language literature of bilateral lung tumor resection for PEH (Table 1): In these reports, the patients ranged in age from 17 to 54 years old, the number of pulmonary operations ranged from 1 to 11 times, the total number of resected tumors ranged 2 to 32 and the observation period after the first operation ranged from 18 months to 24 years. Wedge resections and/or segmentectomies were performed in most of cases, while lobectomy with lymph node dissection was performed in one case (Schattenberg et al. 2007). The surgical approach employed was bilateral thoracotomy (Miettinen et al. 1987, Schattenberg et al. 2007, Baba et al. 2010), median sternotomy (Takahashi et al. 2003), video-assisted thoracoscopic surgery (Kim et al. 2015) or transverse sternotomy (Eguchi & Sawafuji 2015).

Systemic therapy using interferon α 2a (Roudier-Pujol et al. 1994), carboplatin plus etoposide (Pinet et al. 1999), and azathioprine (Marsh et al. 1982) has also been reported.

Table 1. Summary of the previously reported cases of surgery for bilateral pulmonary epithelioid hemangioendothelioma

First author	Year of publication	Age of detection	Sex	Total number of PEH tumors	Total times of Surgery* for PEH	Outcome
Miettinen et al.	1987	17	F	26 (L; 8/R; 18)	11	24 years, died of pneumonia
Takahashi et al.	2003	54	F	8 (L; 3/R; 5)	1	13 years, alive
Schattenberg et al.	2007	25	M	2 (L; 1/R; 1)	1	20 month, alive
Baba et al.	2010	51	F	12 (L; 7/R; 5)	2	9 years, alive
Kim et al.	2015	50	M	3 (L; 1/R; 2)	1	18 month alive
Eguchi & Sawafuji	2015	54	F	32 (L; 11/R; 21)	1	11 years, alive

Abbreviation: PEH, pulmonary epithelioid hemangioendothelioma; M, male; F, female; L, left lung; R, right lung

*Open or thoracoscopic biopsy is excluded.

5. Prognosis

Most patients die of pulmonary insufficiency as a result of increase in the size and/or number of tumor nodules (Amin et al. 2006). The 5-year survival probability is 60% and the cause of death is respiratory failure in 80 % of the cases (Bagan et al. 2006); on the other hand, it has been reported that a 40-year-old woman survived 20 years without specific therapy after having been diagnosed as having PEH based on the detection of bilateral multiple nodular opacities (Teo et al. 1985). Several unfavorable prognostic factors have been identified: presence of respiratory symptoms at presentation, extensive lymphangitic spread, pleural invasion, extensive

intravascular tumor spread, endobronchial tumor spread, interstitial tumor spread, hepatic metastases, and peripheral lymphadenopathy (Dail et al. 1983); pleural effusion, fibrino-fibrous pleuritis with extrapleural proliferation of tumor cells, and presence of spindle-shaped tumor cells (Kitaichi et al. 1981); hemoptysis and hemorrhagic pleural effusion (Bagan et al. 2006). According to a report based on the HEARD registry, there were no significant differences in the survival between patients with single and multiple organ involvement, and the survival rate in PEH patients having lesions with a discrete and defined border is better than of PEH patients having lesions with ill-defined borders (Lau et al. 2011).

6. Discussion

No definitive therapy for PEH has been established until date. Surgery is usually recommended only for patients with a small number of nodules limited to one lung, while PEH often manifests as bilateral multiple nodular opacities.

There are assumed problems in surgery for bilateral lung lesions in patients with PEH: peri-operative risks, decrease in respiratory reserve, and doubts in regard to the survival benefit.

With the advances in anesthesia and perioperative management techniques, bilateral multiple lung tumor resection has become a safer surgery. Thus, where bilateral lung resection for PEH lesions was once considered as contraindicated, it is conceivable that surgery is contemplated now by some as a reasonable treatment option.

In surgical resection of the lungs, post-surgical decrease in the respiratory reserve cannot be avoided. The staging system for primary lung cancer is not applied for case of PEH, therefore, anatomic resection and systematic lymph node dissection are not employed. Fortunately, PEH lesions are small (<2cm diameter) and located in the lung periphery in most cases, therefore, multiple wedge resection or segmentectomy may be preferred in order to minimize resection of functional lung tissue.

Surgery for PEH has not yet been proven by randomized trials to be more effective than non-operative management; however, in most cases of PEH, death results from pulmonary insufficiency as a result of increase in the size and/or number of tumor nodules. There is a possibility that radical PEH tumor resection might delay the potential onset of respiratory failure caused by increase in the sizes of the tumors in some patients. Several cases of bilateral lung tumor resections for PEH have been reported previously. Burden on the patients by frequent surgeries would be a problem, however, high-resolution CT examination and intraoperative manual palpation of lung nodules might contribute to minimizing this risk. Furthermore, accumulation the surgical cases with longer-term follow-up is needed.

7. Conclusion

Bilateral multiple lung tumor resection might be an acceptable therapeutic option for PEH, unless/until effective systemic therapy is established.

Younger patients with a longer life expectancy may deserve this treatment option, in particular. It is necessary to take into account the tumor localization, age and physical condition of the patients, presence/absence of symptoms in considering

bilateral lung surgery for PEH patients
with bilateral lung nodules.

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