Case Report

Successful surgical treatment of epithelioid hemangioendothelioma involving multiple liver lesions and bilateral lung nodules

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ABSTRACT

Epithelioid hemangioendothelioma (EHE) affects many organs, particularly lung and liver, and typically presents as multiple lesions. Treatment for EHE is not yet standardized, but surgery is appropriate when lesions are resectable. In our patient, radiography revealed multiple bilateral pulmonary nodules, and CT showed several liver tumors. The liver masses and those in the right lung were removed during the initial surgery; pathology of hepatic specimens confirmed the diagnosis of EHE. During the second operation, the left lung nodules were excised, and all were EHEs. Surgical removal of multiorgan multinodular EHE is a viable treatment option, especially for young patients.

1. Introduction

Epithelioid hemangioendothelioma (EHE), a tumor derived from vascular endothelial cells, is intermediate in malignancy between hemangoma and angiosarcoma. Histopathologically, atypical cells in EHE are often arranged in a cord-like or foci-like pattern, whereas those in angiosarcoma are often well-developed, and intracytoplasmic vacuoles are often seen in EHE, and mitotic figures are rare. The natural history of EHE is unknown, but it is generally considered to progress slowly. The lung, liver, bones, and soft tissues are considered to be the most common sites of EHE lesions, and a standard treatment has not yet been established for this disease. Here we report a case of EHE involving multiple liver and lung lesions, all of which were surgically resected successfully.

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2. Case report

A 34-year-old man with an unremarkable previous medical history was referred to our hospital for evaluation after a chest X-ray showed a nodular shadow in the right middle lung field. He was asymptomatic at that time. His regular chest X-ray (about once a year), which is conducted by the company he works for, firstly revealed the abnormality. Physical examination revealed a body temperature of 36.7 °C, percutaneous oxygen saturation of 98% (room air), respiratory rate of 16 rpm, blood pressure of 121/70 mmHg, and heart rate of 71 bpm. Laboratory tests revealed a normal leukocyte count (3960 cells/μL) and normal serum level of C-reactive protein (0.1 mg/dL). Hematology showed no findings suggestive of organ damage. Tumor markers (CEA, CA19-9, and SCC), β-D glucan, cryptococcal antigen, Aspergillus antibody, and MAC antibody were all within normal limits. Chest radiographs obtained at presentation (Fig. 1A) showed multiple nodule shadows in both lung fields but predominantly in the right, and chest CT showed multiple nonspecific nodular shadows (Fig. 1B). Abdominal CT revealed multiple nodules scattered throughout the liver (Fig. 1C). We per-

![A](image1)

Fig. 1A. Chest radiographs obtained at presentation showed multiple nodule shadows in both lung fields but predominantly in the right.

![B](image2)

Fig. 1B. Chest CT showed multiple nonspecific nodular shadows.
formed contrast-enhanced CT imaging of his entire body and confirmed that there were only lesions in his liver and lungs. Suspecting a metastatic lung tumor from the gastrointestinal tract, we performed an upper endoscopy and a lower endoscopy with no abnormal findings. Gastroenterology consultation and liver biopsy performed at this time did not yield a diagnosis. Our patient then underwent laparoscopic partial liver biopsy; histopathology revealed EHE. Eight months after the laparoscopic evaluation, follow-up CT showed both new and residual lesions in the liver, and repeat chest CT showed enlargement of the pulmonary nodules (Fig. 2). PET-CT imaging was performed prior to liver surgery. The multiple nodules in his lungs showed only faint accumulation on PET (SUVmax 0.87), and many of the lesions were small in size and difficult to evaluate on PET. The lesions noted in his liver showed relatively strong accumulation (SUVmax 2.84) on PET. There were no obvious significant PET-accumulated lesions in his other systemic organs. At that time, our patient underwent cholecystectomy and removal of the liver enlargement area + partial resection, followed by excision of the entire right middle lung lobe and partial resection of the right S3 to S8 regions. During a second procedure at 1 month after the right lung operation, the left S8 lung area was removed, and partial resection of the lower lobe was performed. Consistent with the liver specimens, histopathology of lung tissue confirmed EHE.

Pathologically, lesion margins were round, square, or polyhedral, and tumors contained proliferating epithelial-like cells with abundant cytoplasm covering the vitreous interstitium (Fig. 3A). The centers of tumors were prominent, with vitreous interstitium or
a cartilage-like matrix, often accompanied by necrosis. Immunohistochemistry yielded positive staining for CD31, CD34 (Fig. 3B and C) and Factor VII, and samples were negative for AE1/AE3 signals. The Ki-67 index, which indicates the expression rate of the Ki-67 protein and thus the proliferative capacity of the tumor cells, was 4.6% (Fig. 3D). The tumor border was demarcated, and the tumor had grown to fill the alveolar space. It comprised cords or nests within myxochondroid or hyaline stroma. The tumor cells showed plump or epithelioid with abundant eosinophilic cytoplasm. It had intracytoplasmic vacuoles, and some of these contained erythrocytes. These histological findings and the positivity of CD34 were characteristic of EHE, so we diagnosed it as EHE. Every 3–6 months we follow up his images with a thoracoabdominal CT. As for the tumor in the liver, it was found to recur 10 months after the liver surgery, and the patient was reoperated and is under follow-up, but no recurrence has been found so far. Micro nodule shadows in the lungs are being followed up, but it has already been two years since the right lung surgery.

3. Discussion

Based on the multiple nodular shadows in his lungs and multiple shadows in his liver, we initially considered metastatic lung or liver tumor from a gastrointestinal tumor, such as stomach or colon cancer, as the primary differential. Next, we also had in mind sarcoidosis as a disease involving the lungs and liver. Cryptococcosis was also on our list of infectious diseases. EHE had previously been thought to derive from alveolar epithelium with intravascular extensions and therefore was known as intravascular bronchioloalveolar tumor (Dail Liebow et al., 1975), but this neoplasm is now considered to arise from vascular endothelial cells. Currently low-grade angiogenic tumors of soft tissues showing the characteristic histology are labeled EHE, and EHE and intravascular bronchioloalveolar tumor are considered to be the same entity. [1] In addition, pulmonary epithelioid hemangioendothelioma—EHE that develops in the lung—accounts for approximately 60 cases of EHE in Japan annually.

Making up 63% of all cases, frequent sites of EHE include lung, thoracic membranes, mediastinum, heart, liver, bone, soft tissue, and brain, and lesions can be found concurrently in multiple organs, [2] as occurred in the case we present. But which tissue was the

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Fig. 3B. The centers of tumors were prominent, with vitreous interstitium or a cartilage-like matrix, often accompanied by necrosis. Immunohistochemistry yielded positive staining for CD31, CD34.
Fig. 3C. The centers of tumors were prominent, with vitreous interstitium or a cartilage-like matrix, often accompanied by necrosis. Immunohistochemistry yielded positive staining for CD31, CD34.

Fig. 3D. The Ki-67 index, which indicates the expression rate of the Ki-67 protein and thus the proliferative capacity of the tumor cells, was 4.6%.

source of the primary lesion from which the rest metastasized or whether the nodules arose multicentrically is difficult to ascertain. [3] Until now, EHE was thought to occur multicentrically. [4-7] However, one group recently used genetic commentary to prove the monochromaticity of multinodular EHE and support the possibility that EHE can arise through metastatic expansion.[8]).

In regard to imaging features, EHE typically presents as multiple nodules with clear boundaries and a diameter of 2 cm or less; it is rarely found as a single nodule shadow. In PET-CT studies, FDG accumulation varies widely and may be particularly low in cases with small nodules or slow growth. [9] Consistent with this pattern, CT images of our current case lacked significant FDG accumulation because the nodules were small. Furthermore, again likely because of the typically small tumor size, surgical lung biopsy is more useful than bronchoscopy for diagnosis of EHE.

Pathologically speaking, a vitrified substrate fills the main component in the central part of EHE lesions, and the tumor cells proliferate in an alveolar-filling manner along the margins. Immunohistochemically, EHEs characteristically are positive for Factor VIII-related antigens, CD31, and CD34, which are vascular endothelial markers.[10]) Furthermore, molecular genetic studies have revealed t(1; 3) (p36.3; q25) translocation in more than 90% of classical EHE, involving CAMTA1 on chromosome 1p36.23 and WWTR1 on chromosome 3q25 are the involved genes.[11]).

Currently, there is no standard treatment for EHE. When EHE presents as a single lesion, resection is performed. Surgery is similarly applicable when multiple nodules are present, as long as lesions are accessible. In symptomatic cases, appropriate supportive care is provided. For patients with unresectable systemic lesions, cytotoxic anticancer agents such as carboplatin and etoposide and chemotherapy with IFN-α and bevacizumab have been provided [12-14]), but none has been shown to be effective.

The average prognosis for cases of EHE is 4.6 years, but some patients have died within a few weeks after diagnosis and others have survived for 10 years or more. [15]). Features indicative of a poor prognosis include symptomatic cases at the time of diagnosis, tumor diameter of 3 cm or more, and a Ki-67 index of 10% or more. [16]) Our patient was asymptomatic, had a Ki-67 index of 4.6%, and, although he had multiple tumors, all diameters were less than 1 cm. We anticipate that he will have a relatively long survival, but careful follow-up is required.
4. Conclusion

In this case, multiple nodular shadows were found in multiple organs, but considering the possibility that they occurred in multiple centers, a complete resection was performed by surgical treatment.

For cases with good lung function, surgical treatment may be considered even for multiple lung lesions.

Learning points

When we encounter multiple nodules in the lungs or multiple lesions in the liver, we should scrutinize them with EHE in mind, as well as metastatic tumors.

There is no established drug treatment for EHE, and it is better to go with the idea of surgery whenever possible.

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Declaration of competing interest

None.

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