Endotracheal Metastasis and Superior Vena Cava Obstruction from Hepatocellular Carcinoma: a Case Report

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บทคัดย่อ: การลุกลามของมะเร็งตับเข้ามาในหลอดลมใหญ่และกดทับเส้นเลือดซุพีเรียเวนาคาวา: รายงานผู้ป่วย

ศศิธร อินทร์แก้ว พ.บ.
โรงพยาบาลมะเร็งลพบุรี ตำบลทะเลชุบศร อำเภอเมือง จังหวัดลพบุรี 15000

ผู้ป่วยชายไทยอายุ 49 ปี มาโรงพยาบาลด้วยอาการสำคัญคือไอมีเสมหะปนเลือด หน้าและลำตัวสวนบนบวมมา 1 เดือน แข็งแรงดี ไม่มีประวัติโรคประจำตัวมาก่อนหน้านี้ ภาพเอกซเรย์คอมพิวเตอร์ทรวงอกพบว่ามีต่อมน้ำเหลืองข้างหลอดลมโตและมีการลุกลามเข้าไปในหลอดลมใหญ่และมีการกดทับเส้นเลือดดำใหญ่ ซุพีเรียเวนาคาวา ผู้ป่วยได้รับการส่องกล้องหลอดลมพบก้อนในหลอดลมและได้ทำการตัดชิ้นเนื้อส่งตรวจทางพยาธิวิทยาและย้อมติดสีที่เฉพาะเจาะจงกับมะเร็งตับ ผู้ป่วยรายนี้จึงได้รับการวินิจฉัยว่าเป็นมะเร็งตับระยะที่ 3 (advanced stage HCC) ที่มีการลุกลามไปต่อมน้ำเหลืองมิดิแอสตินัมและหลอดลมใหญ่ ร่วมกับมีอาการแสดงของการกดทับเส้นเลือดดำใหญ่ซุพีเรียเวนาคาวา (SVCO) ผู้ป่วยได้รับการรักษาฉายแสงเร่งด่วนและได้รับยา sorafenib ที่เป็นการรักษาเฉพาะมะเร็งตับระยะที่ 3 ผู้ป่วยเสียชีวิตหลังจากได้รับการรักษาด้วยยา sorafenib มา 8 เดือน

คำสำคัญ: การลุกลามของมะเร็งมาหลอดลมใหญ่ การลุกลามของมะเร็งตับ การกดทับเส้นเลือดซุพีเรียเวนาคาวา

Abstract

Endotracheal metastasis from hepatocellular carcinoma are very rare. A 49-years-old man was admitted to the hospital with a 1-month history of cough, blood streak sputum and swelling of upper part of body. The patient had no underlying disease. Radiological findings were huge mediastinal lymphadenopathy at lower paratrachea with direct invasion to endotracheal and complete compress superior vena cava (SVC). Bronchoscopic with endotracheal lesion biopsy was done and the tissue pathology positive staining for hepatocyte paraffin 1 (Specific immunohistochemistry for HCC). Final diagnosis was advanced hepatocellular carcinomas with mediastinal lymph node and endotracheal metastasis and SVC obstruction. The patient received immediated radiation for life threatening conditions and sorafenib for specific treatment in advanced stage HCC. He died at 8 months after received sorafenib.

Keywords: Endotracheal metastasis, Hepatocellular carcinoma metastasis, Superior vena cava obstruction

Introduction

Endobronchial metastasis (EBM) secondary to extrthoracic solid malignancies are seen rarely, about 2% in autopsy case[1-4]. The extrathoracic malignancy that have been reported to have spread to the trachea and bronchi most common in breast cancer, colon cancer and kidney cancer[1, 5, 6]. Hepatocellular carcinoma with endobronchial metastasis is very rare[7, 8]. Search for Pubmed by keyword “Enodobronchial metastasis” and “Hepatocellular carcinoma” From 1980 to 2020, only 9 cases were reported.

Most common cause superior vena cava obstruction obstruction (SVCO) is intrathoracic malignancies (60-80%) [10]. Non-small cell lung cancer (NSCLC) about 22-57% of all malignant causes, followed by SCLC (10-39%) and NHL (1-27%)[9, 10]. Hepatocellular carcinoma with mediastinal metastases causing superior vena cava obstruction is very rare. Search for Pubmed by keyword “Superior vena cava obstruction” and “Hepatocellular carcinoma” From 1988 to 2020, only 10 cases were reported.

This paper report first case of hepatocellular carcinoma with mediastinal lymph node metastasis causing superior vena cava obstruction and endotracheal metastasis in Thailand was describe symptom, sign, diagnosis, clinical course, and management.

Case Report

A 49-year-old Thai male good general health in previously. He present with cough with bloody sputum and dyspnea on exerting for 1 month. He had face, neck, upper thorax, both arms swelling and headache. He had a history of smoking 20 cigarettes a day for 30 years and tattoo on his arms for 30 years. He denied history of blood transfusion, intravenous drug used, and history of malignancy in his family. Physical examination showed puffy eyelid, face swelling, non-pitting edema of both arms, superficial vein dilated and sign of chronic liver disease, that are palmar erythema, gynecomastia and spider nevi. Respiratory system examination showed expired stridor.

Laboratory test at admission were complete blood count (CBC), blood urea nitrogen (BUN), creatinine (Cr), liver function test (LFT) and coagulogram revealed normal. Anti-HIV were non-reactive, HBsAg negative and Anti-HCV positive. Alpha fetoprotein (AFP) showed high level (2,805 ng/ml; normal range was 0-13.6 ng/ml)

Plain X-ray chest (Figure1) revealed elongate soft tissue density mass at right paratrachea. Irregular internal lumen of lower trachea. Computer tomography (CT) of the chest (Figure2) showed multiple enhancing soft tissue mass along right paratrachea, subcarina, subaortic, left hilar region, size up to 5.5 * 4.4 cm, causing mass effect to compress and leftward shifting of the lower trachea. Soft tissure bulging into the trachea anterior to the carina. Multiple pulmonary nodules. Abnormal filling defect in enhancement in Superior vena cava (SVC) and left brachiocephalic vein. These finding could be superior vena cava obstruction (SVCO) suspected from tumor thrombosis. Tripple-phase abdomen computer tomography (Figure 3) showed Liver cirrhosis with multiple varices and collateral vessels. Liver parenchyma defect at hepatic segment V and VIII with a rather wedge-shaped hypodense lesioninvolving hepatic segment IV/V and subcapsular retraction which apex point to liver hilum are noted. Multiple small arterial enhancing/delayed washout nodule along the liver parenchyma defect and subcapsular retraction size up to 2 cm. These finding could be confluent hepatic fibrosis or post-surgical change with small hepatocellular carcinoma.

Virtual bronchoscopy was done. Bronchoscopic (Figure4) showed endotracheal mass moving according to breathing at lower trachea causing trachea 90% narrowing (nearly complete obstruction), cannot pass bronchoscope to evaluated below these mass and biopsy were taken from endotracheal lesion.

A hematoxylin-eosin staining (Figure 5) revealed sheets of malignancy cell among stroma. Those malignancy cell are large polygonal to round cell with enlarged hyperchromatic nuclei. Some nuclei cantain nucleoli. The cytoplasm is moderate in amount. No definite gland or keratin pearl formation is seen. Pathologic diagnosis is poorly differentiated carcinoma. The stained immunohistochemistry of malignancy cell (Figure 6) showed negative stained of cytokeratin (CK), Tumor protein 63 (P63), thyroid transcription factor-1 (TTF-1), synaptophysin, Chromogranin, CD34, Napsin A, CD56. The tumor cells stained strongly immunohistochemically with hepatocyte (Dako Denmark, 1:25, monoclonal mouse anti-human). The endobronchial metastatic hepatocellular carcinoma was diagnosed. The pathologist diagnosis was made without knowledge of clinical data.

Clinical diagnosis in first admission of superior vena cava obstruction and categorized grading system for SVCO was grade 3 due to progressive headache; the patient was treated with palliative radiation immediatedly. After confirmation of endotracheal metastasis from hepatocellular carcinoma; the patient was treated molecular targeted therapy (sorafenib). He died after 8 months of specific treatment.

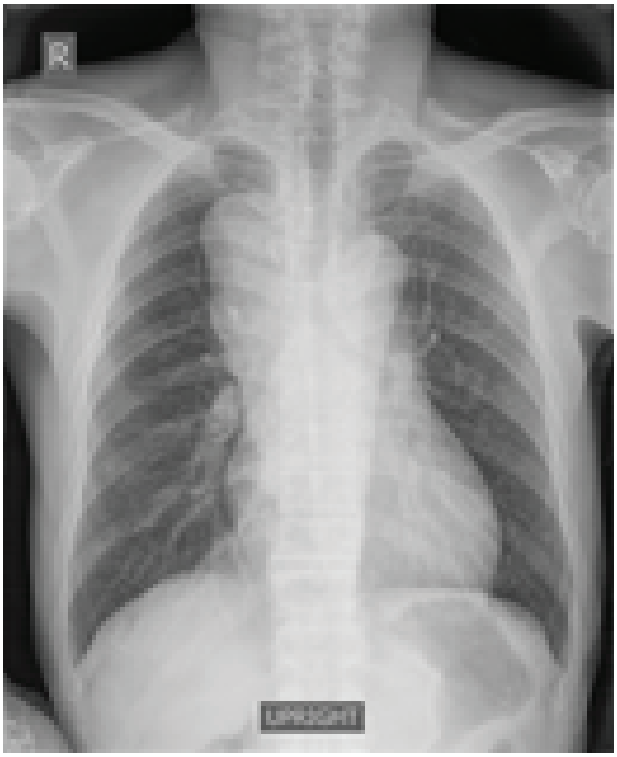


Figure 1 Plain X-ray chest revealed elongate soft tissue density mass at right paratrachea without displacement of trachea. Irregular internal lumen of lower trachea suspected from endotracheal lesion.

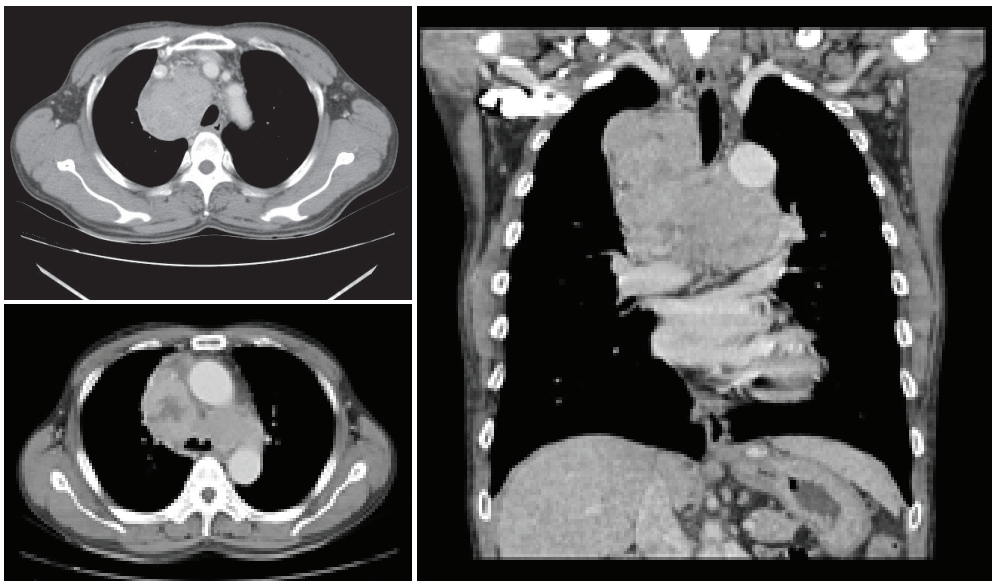


Figure 2 Computer tomography of chest showed multiple enhancing soft tissue mass along right paratrachea, subcarina, subaortic, left hilar region, size up to 5.5 * 4.4 cm, causing mass effect to compress and leftward shifting of the lower trachea. Soft tissure bulging into the trachea anterior to the carina. Abnormal filling defect in enhancement in Superior vena cava (SVC) and left brachiocephalic vein. These finding could be superior vena cava obstruction (SVCO) suspected from tumor thrombosis.

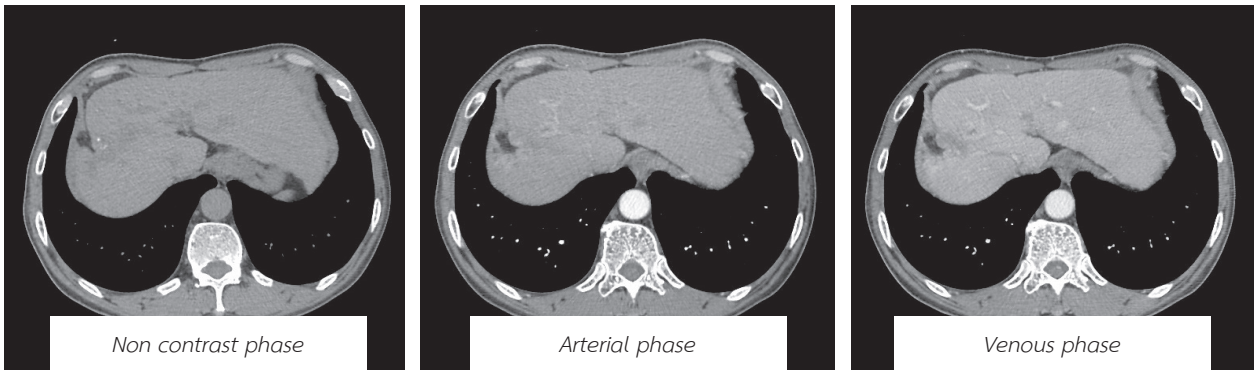


Figure 3 Tripple-phase abdomen CT showed liver cirrhosis with multiple varices and collateral vessels. Liver parenchyma defect at hepatic segment V and VIII with a rather wedge-shaped hypodense lesioninvolving hepatic segment IV/V and subcapsular retraction which apex point to liver hilum are noted. Multiple small arterial enhancing/ delayed washout nodule along the liver parenchyma defect and subcapsular retraction size up to 2 cm. These finding could be confluent hepatic fibrosis or post-surgical change with small hepatocellular carcinoma.

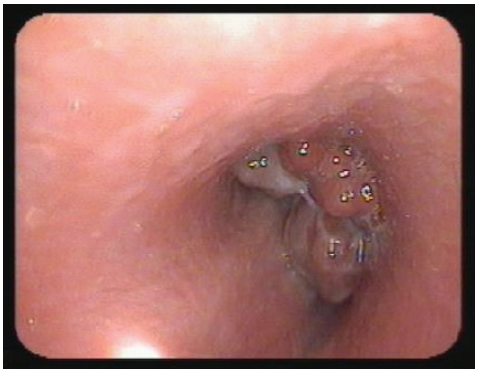
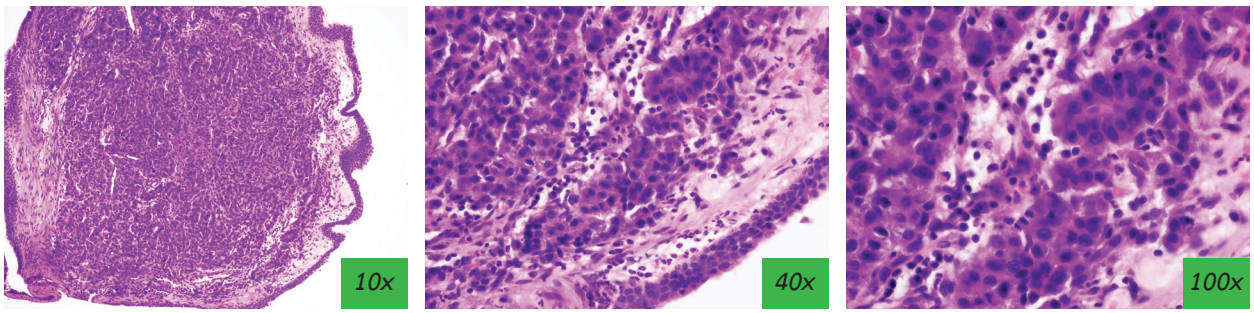


Figure 4 Bronchoscopic finding showed endotracheal mass moving according to breathing at lower trachea causing trachea 90% narrowing (nearly complete obstruction), cannot pass bronchoscope to evaluated below these mass and biopsy were taken from endotracheal lesion.



A B C

Figure 5 H&E staining revealed sheets of malignancy cell among stroma. Those malignancy cell are large polygonal to round cell with enlarged hyperchromatic nuclei. Some nuclei cantain nucleoli. The cytoplasm is moderate in amount. No definite gland or keratin pearl formation is seen. Pathologic diagnosis is poorly differentiated carcinoma.

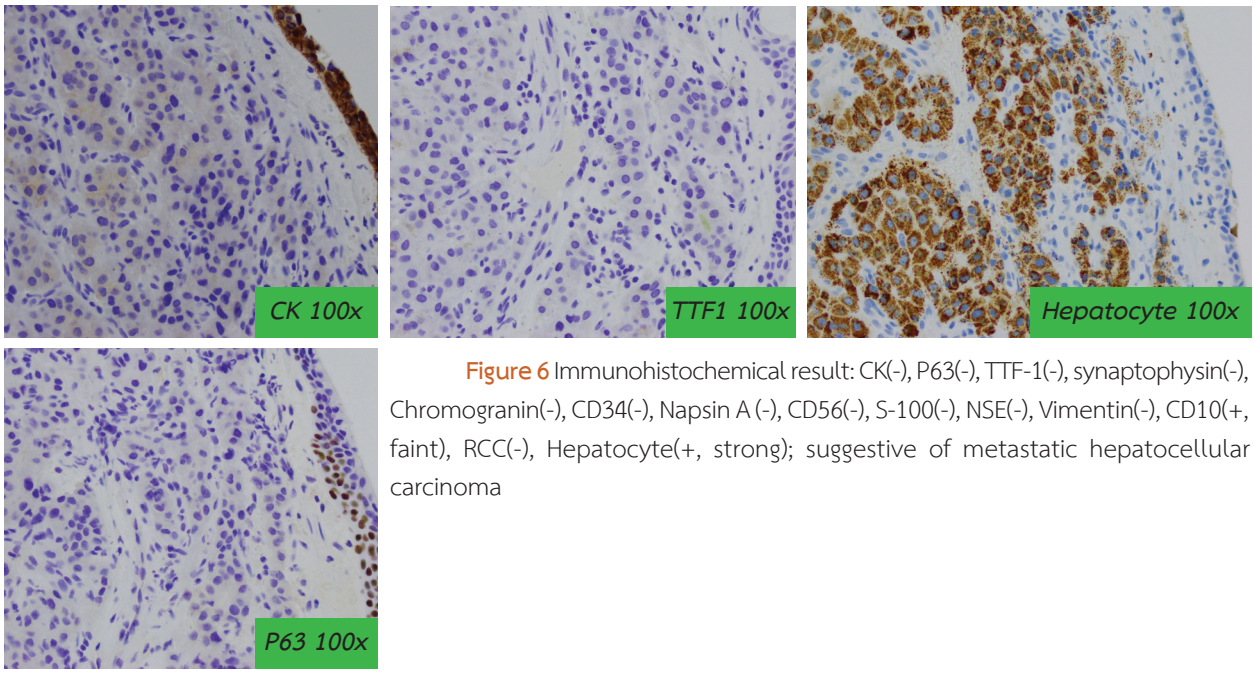


Figure 6 Immunohistochemical result: CK(-), P63(-), TTF-1(-), synaptophysin(-), Chromogranin(-), CD34(-), Napsin A (-), CD56(-), S-100(-), NSE(-), Vimentin(-), CD10(+, faint), RCC(-), Hepatocyte(+, strong); suggestive of metastatic hepatocellular carcinoma

Discussion

The superior vena cava obstruction (SVCO) comprises various symptoms due to occlusion of the SVC, causing from pathological conditions. The resulting increased venous pressure in the upper body may cause edema of the head, neck, and upper extremities, often associated with cyanosis, plethora, and distended subcutaneous vessels. SVCO often cause life-threatening condition.

Most common cause SVCO is intrathoracic malignancies (60-80%)[10]. Non-small cell lung cancer (NSCLC) about 22-57% of all malignant causes, followed by SCLC (10-39%) and NHL (1-27%)[9, 10]. Rare malignant causes include germ cell neoplasms, and thymoma, leiomyosarcomas of the mediastinal vessels, plasmacytomas, metastatic disease. Hepatocellular carcinoma with mediastinal metastases causing superior vena cava obstruction is very rare. Search for Pubmed by keyword "Superior vena cava obstruction" and "Hepatocellular carcinoma" From 1988 to 2020, only 10 cases were reported.

SVC carries one-third of the blood return to the heart, that drainage from the head, arms, and upper thorax. SVC is thin walled and low venous pressure, that causing susceptible to compression by adjacent masses[11]. If SVCO occurs slowly, patients may asymptomatic because developing of collateral vein. In contrast, rapidly SVCO, the patients always present many symptoms[12]. The most common symptoms and sign of SVCS include neck swelling (100 %), dyspnea (54–83 %), swelling of the trunk and/or upper extremities (38–75 %), facial swelling (48–82 %), chest pain (15 %), cough (22–58 %), dilated chest vein collaterals (38 %), weight loss (10–31 %), jugular venous distension (27 %), phrenic nerve paresis (16.2 %), plethora (13 %) and dysphagia (10–13 %)[12]. Symptoms typically have a gradual onset.

Multi-slice CT scans usually use for initial evaluation of SVCO and can detect prior to symptom was present[13, 14]. For patients allergic to contrast dye or with difficult venous access, further MRV is proper this condition.

Urgent management for SVCS patients determining by Proposed Grading System for Superior Vena Cava Syndrome (Yu et al.'s classification)[15]. Each sign or symptom due to SVCO and the effects of cerebral or laryngeal edema or effects on cardiac function. Symptoms caused by other factors (for example; vocal cord paralysis, lung atelectasis, mediastinum shift from pleural effusion) should be not be considered. The propose grading systems are grade 0 shows radiographic SVCO in the absence of symptoms; grade 1 shows edema in head or neck (vascular distention), cyanosis, plethora; grade 2 shows edema in head or neck with functional impairment (mild dysphagia, cough, mild or moderate impairment of head, jaw or eyelid movements, visual disturbances caused by ocular edema); grade 3 shows mild or moderate cerebral edema (headache, dizziness) or mild/moderate laryngeal edema or diminished cardiac reserve (syncope after bending); grade 4 shows significant cerebral edema (confusion, seizure) or significant laryngeal edema (stridor) or significant hemodynamic compromise (syncope without precipitating factors, hypotension, renal insufficiency).

In SVCO patient present with grade 3, 4 of grading system required prompt management and rapid empiric treatment with radiation, stenting, and/or chemotherapy may be indicated even before biopsy[16] to minimize respiratory and cardiac complications. Immediate RT is not indicated as first line treatment in emergent cases of SVCO if vascular stenting is feasible, as stenting has been shown to provide faster symptom resolution[17]. Furthermore, obtaining an accurate histologic diagnosis prior to starting RT allows for optimum treatment of the causative malignancy[18]. In this case report the patient present of gradual onset of symptom, that he present with progressive headache classified as grade 3 of grading system and impending large airway obstruction due to endotracheal mass which requires urgent treatment. In Lopburi Cancer hospital had no equipment for vascular and airway stent, so the patient treated by immediate radiation after endotracheal mass biopsy was done (not wait for result of tissue histopathology). Radiation protocal vary in radiation dose and day of radiation in each institute to get total radiation dose 3,000-5,000 cGy in period. The subjective response rate was 77 and 91 % response rate at 3–4 and 7 days after treatment[19]. Other management for reduce patient symptoms are elevate his head[20], fluid restriction, diuretics and/or supplemental oxygen[21]. In this patient had received 300 cGy for 10 days to get 3,000 cGy in period and the patient had initial improvement of severe headache and no stridor after 1 week of radiation.

The median survival of all SVCO patient included in the review was 1.5-10 months, 1-year overall survival (OS) was 24 %, and 5-year OS was 9 %[18, 22]. The average life expectancy for patients who present with malignancy-related SVC syndrome is 6 months, although the prognosis is quite variable depending on the type of malignancy.

Endobronchial metastasis (EBM) secondary to extrthoracic solid malignancies are seen rarely, about 2 % in autopsy case[1-4,23]. The extrathoracic malignancy that have been reported to have spread to the trachea and bronchi most common in breast cancer, colon cancer and kidney cancer[1, 5, 6, 24]and there are some case report in ovarian cancer, thyroid cancer[25-27], uterine cancer, prostate cancer[28, 29].

In this report show very rare case of hepatocellular carcinoma with endobronchial metastasis[7, 8]. Majority of patients with the diagnosis of hepatocellular carcinoma have distant metastases within the first year. The most frequent locations are: lungs, bones and adrenal glands[30]. Search for Pubmed by keyword. "Enodobronchial metastasis" and "Hepatocellular carcinoma" From 1988 to 2020, only 9 cases were reported. Symptoms, signs and radiography including bronchoscopic finding cannot distinguish whether primary lung cancer or extrapulmonary cancer. Therefore, biopsy and special staining are needed to assist in the differential diagnosis and to select further treatment options.

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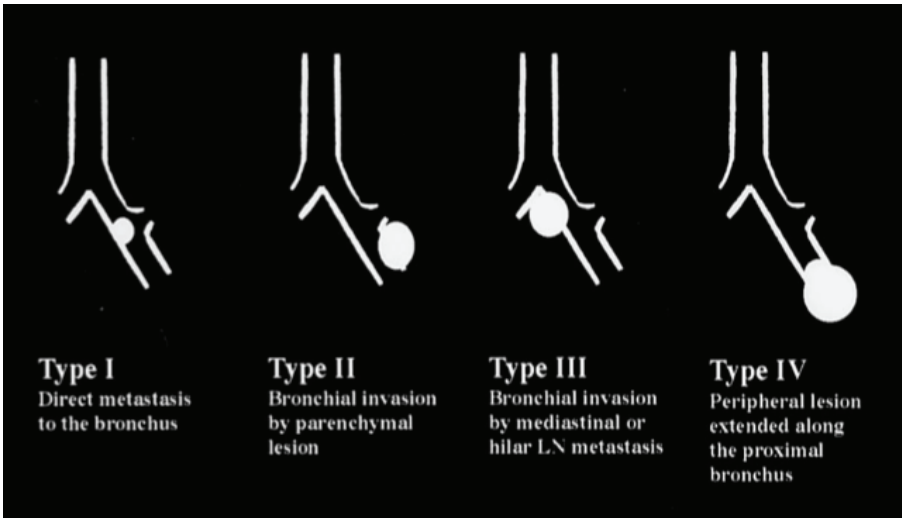
The clinical presentation and radiological imaging of endobronchial metastases[8] are similar to primary bronchogenic carcinoma. Most patients suffer from cough, hemoptysis, chest pain, dyspnea and respiratory failure. Kiryu[24] proposed four developmental modes of tracheobronchial metastases: type I, direct metastasis to the bronchus; type II, bronchial invasion by a parenchymal lesion; type III, bronchial invasion by the mediastinal or hilar lymph node metastasis; and type IV, peripheral lesions extended along the proximal bronchus.



In this case from Chest CT showed intrathoracic mediastinal node direct invasion to endotracheal that classified as type III. However, we haven't been able to definite diagnosis in this patient, still wait for histopathology. In that situation the patient present with productive cough plus bloody sputum and history of heavy smoking, from imaging showed huge mediastinal mass direct invasion to trachea that we give provisional diagnosis at first visit was lung cancer with SVCO. The symptom classified as severe grade of SVCO and impending large airway obstruction, we decided give immediate radiation with expectation the lung cancer was good response to radiation that may be improve of two conditions.

The diagnosis HCC in cirrhotic patient usually us non-invasive method was typical hallmark in multiphase CT or contrast-enhanced MRI, that showed nodule > 1cm with arterial phase hyperenhancement (APHE) with washout in delayed phase[31]. In this case the patient present with chest symptom, imaging and bronchoscopic finding showed endotracheal lesion, the biopsy endotracheal lesion was done and specific immunohistochemistry (hepatocyte paraffin 1[29] was performed , we give the definite diagnosis was advanced stage hepatocellular carcinoma (HCC) followed by BCLC staging system with mediastinal lymph node and endotracheal metastasis.

The incidence of mediatinal lymph node metastasis from HCC has been reported to be 4-5%[32]. The first route is from the left hepatic lobe via anterior phrenic lymph nodes to the parasternal or subcarinal lymph nodes; the second, from the liver through the hepatic falciform ligament to the parasternal or paratracheal lymph nodes; and the third, from the right hepatic lobe through the right triangular ligament to the paratracheal lymph nodes.[32] Current managements for these patients are oral administration of sorafenib and possibly transarterial chemoembolization for the hepatic tumors if the patient has sufficient remaining liver function[33]. The most frequent metastatic sites are the lungs, lymph nodes, bones and adrenal glands[34]. Metastases in the mediastinum are rare.

The treatment options for mediastinal metastases of HCC was regional lymphadenectomy, radiofrequency ablation. However, the majority of extrahepatic lymph node metastases of HCC are multiple and are not suitable for resection or radiofrequency ablation, as was the case with the present patient. Radiation therapy was recently technique use in extrahepatic metastasis[35]. In a previous study, a major response to a radiation dose of ≥45 Gy was observed, with a dose-response relationship determined for local control radiotherapy[36]. In this case report after radiation, the patient was gradually improvement of symptom cause by both SVCO and radiosensitive HCC.

Sorafenib (multi-tyrosine kinase inhibitor) has been shown to be effective in the treatment of advanced or metastatic HCC [23, 37, 38]; however, it is indicated for patients well-preserved liver function (Child-Pugh A class) and advanced stage tumors (Barcelona Clinic Liver Cancer C)[39]. Which our patient was in the indications, so he received sorafinib sorafenib therapy. The median overall survival (OS) times of advanced HCC are 6.5-10.7 months[38, 40]. In case report, the patient alive 8 months after receive sorafenib.

Conclusion

Accurate and comprehensive history with complete physical examination may help for the diagnosis. As in this patient from physical examination showed sigh of chronic liver disease that remind our team the final diagnosis will association with underlying chronic liver disease. From imaging and bronchoscopic finding showed endotracheal lesion, primary lung cancer is most likely but not exclude other malignancy, so we give biopsy the endotracheal lesion for tissue histopathology and staining for immunohistochemistry. Final diagnosis was Advanced stage HCC with mediastinal lymph node and endotracheal metastasis with SVCO. In addition, complete history and physical examination in this case found progressive severe headache and stridor, which life threatening conditions cause this patient received immediate treatment before its get worse.

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