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Case Report

A Rare Case of Hepatocellular Carcinoma with Metastasis to The Thyroid

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Abstract

Background: Liver cancer is among the top five causes of cancer death globally. Hepatocellular Carcinoma (HCC) accounts for up to 90% of primary liver neoplasms in adults. The incidence of thyroid me-tastasis from HCC is rare and estimated from 0.8 to 12%. This report describes a 51-year-old man presenting with hypercalcemia and known metastatic HCC with new metastasis to the thyroid gland.

Case Report: A 51-year-old male was admitted due to symptomatic hypercalcemia. His medical history included HCC with metastasis to the retroperitoneal lymph nodes diagnosed one year prior. Computed tomography revealed an enlarging liver mass, diffuse lymphadenopathy and many osseous lytic lesions. Ultrasound of the neck revealed abnormal right cervical lymph nodes and a heterogeneous mass replacing the right thyroid gland. Biopsy of the right cervical lymph node immunohistochemical stained positive for PAN-K, Glypican-3, HepPar1 and Anti-Arginase and negative for p40 and CEA-poly, supporting the diagnosis for metastatic HCC. His hospital course was complicated by dysphagia, spontaneous bacterial peritonitis and acute-on-chronic liver failure. Despite aggressive resuscitation, he continued to decline and ultimately pursued hospice care.

Conclusion: This case illustrates the need to have a high index of suspicion for thyroid metastasis in HCC patients presenting with a new-onset cervical mass, dysphagia or hypercalcemia. Metastatic cancer to the thyroid gland is generally considered a poor prognostic factor, as seen in this case with the rapid decline. This case demonstrates an extremely rare presentation of HCC with metastasis to the thyroid gland.

Keywords: Hepatitis B (D006509); Liver Neoplasms (D008113); Thyroid Neoplasms (D013964); Carcinoma, Hepatocellular (D006528)

Introduction

Liver cancer is estimated to be the sixth most diagnosed cancer and among the top five leading causes of cancer death globally [1]. The increasing incidence of liver cancer represents a significant health concern as it results in substantial morbidity and mortality. A systemic review of cancer statistics from 185 countries predicted a 55% increase in incidence of liver cancer globally by 2040 [2]. In the United States, the incidence of primary liver cancer is estimated to be 8.6 per 100,000 individuals per year, with a 5-year survival rate of 21% [3]. Hepatocellular Carcinoma (HCC) is the most common histological type of primary liver neoplasm identified in adults, accounting for up to 90% of cases [4]. The major risk factors for developing HCC include hepatitis B and C viral infections, heavy alcohol consumption, Non-Alcoholic Fatty Liver Disease (NAFLD), Non-Alcoholic Steatohepatitis (NASH) and metabolic syndrome [4]. The pathophysiology of HCC is complex, but alterations in the cellular microenvironment resulting from underlying chronic liver disease play a crucial role in the development of the neoplasm and its progression to metastatic disease [4].

Screening occurs in patients with identifiable risk factors with abdominal ultrasounds and serum Alpha Fetal Protein (AFP) levels. Suspicious findings prompt imaging with quadruple phase CT or MRI with contrast to confirm the diagnosis [4]. Treatment depends on the size and stage of disease. Generally, patients with early-stage disease are candidates for resection or transplant, while those with advanced or metastatic disease receive systemic therapies with palliative intent [4].

As with many malignancies, the likelihood of metastasis from HCC increases as the disease progresses. Metastasis can occur via direct tumor invasion, hematogenous or lymphatic spread [5]. The most common sites of metastasis are the lung, abdominal lymph nodes, bones and the adrenal glands [5,6]. Metastatic HCC to the thyroid gland is rare and few cases have been previously described in the literature [7-13]. The incidence of thyroid metastasis from HCC is estimated to range from 0.8 to 12% based on autopsy studies [11]. This case demonstrates a rare example of hepatocellular carcinoma with metastasis to the thyroid and cervical lymph nodes in a 51-year-old male presenting with hypercalcemia.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

Case Report

A 51-year-old male presented to the emergency department at the recommendation of his oncologist due to hypercalcemia seen on outpatient lab work. His past medical history was significant for obesity status-post gastric sleeve performed four years prior to presentation, alcoholic cirrhosis, chronic hepatitis B infection noncompliant with Entecavir and HCC with metastasis to retroperitoneal lymph nodes. His HCC was diagnosed one year previously with Computed Tomography (CT) of the abdomen and pelvis revealing an 8 cm single liver lesion and an Alpha Fetoprotein Level (AFP) of 35,728 ng/mL (normal: 0-40 ng/mL). Based on the patient's clinical findings, he was diagnosed with advanced stage C metastatic HCC per the Barcelona classification and was treated without initial liver biopsy. He had completed one cycle of palliative radiation for pain management. Five days prior to admission, he underwent placement of a right chest port with plans to begin palliative immunotherapy with Atezolizumab and Bevacizumab.

At the time of admission, the patient was presented with confusion, abdominal pain, generalized weakness, myalgias and constipation. The patient was afebrile with temperature 97.6˚F, tachy-cardic at 130 beats per minute and blood pressure of 140/97 mmHg. He was saturating 100% on room air. Physical exam revealed a cachectic male with diffuse abdominal tenderness, abdominal distension and right-sided anterior cervical adenopathy. There was no evidence of thyromegaly or significant organomegaly. His laboratory evaluation was significant for hypo-natremia with sodium of 129 mmol/L (normal: 136-145 mmol/L), normocytic anemia with hemoglobin 11.8 g/dL (normal: 12.6-16.7 g/dL), platelets of 123 x 103 /uL (normal: 139-361 x 10 3/uL) and hypercalcemia with calcium of 14.1 mg/dL corrected to 14.9 mg/dL (normal: 8.4-10.2 mg/dL) for albumin of 3.0 g/dL (normal: 3.5-5.0 g/dL). His liver function tests were sig-nificant for total bilirubin of 1.3 mg/dL (normal: 0.2-1.2 mg/dL) and AST of 88 U/L (normal: 5-34 U/L). His parathyroid hormone was decreased <4 pg/mL (normal: 12-88 pg/mL). His al-pha-fetoprotein was measured at >80,000 ng/mL. His INR was 1.2. CT head was unremarkable. Abdominal ultrasound revealed moderate volume ascites in the right and left upper abdominal quadrants. Patient underwent paracentesis and fluid analysis indicated spontaneous bacterial peritonitis (SBP). He was treated with ceftriaxone 2 g daily. The patient was started on zoledronic acid, calcitonin and intravenous fluid resuscitation with 0.9% saline to address hypercalcemia of malignancy.

CT of the abdomen and pelvis revealed interval increase in size of the left liver mass now meas-uring 3.6 x 3.4 cm compared to 1.9 x 1.7 cm two weeks prior. CT also revealed lymphadenopathy in the chest and abdomen with the largest lymph node measuring 4.4 x 4.1 cm and innumerable lytic metastatic lesions throughout the visualized osseous structures with the largest at T8 measuring 1.6 x 1.4 cm. There was a hypodense lesion on the posterior right lobe of the liver measuring 5.9 x 4.6 cm that was similar to the previous examination and splenomegaly (Fig. 1). Further evaluation of new neck mass was pursed with an ultrasound that revealed multiple morphologically abnormal lesions in the right-side level 2, 3 and 4 lymph nodes. The right thy-roid lobe appeared to be replaced by a heterogenous mass measuring 5.3 cm in the maximal dimension. The left thyroid appeared normal. Considering the rapid increase in disease burden seen on CT, the image findings and new clinical signs were concerning for metastatic HCC versus new primary thyroid malignancy. The thyroid was not biopsied due to concern of airway compromise from thyroid mass hemorrhage. To aid in staging, prognosis and treatment, the patient underwent ultrasound-

guided core biopsy of a lymph node on the right side of his neck. The tumor cells stained positive for PAN-K, Glypican-3, HepPar1 and anti-arginase and were negative for p40 and CEA-poly (Fig. 2,3) confirming the diagnosis of HCC metastasis to right cervical lymph nodes. He was discharged and planned to follow up with medical oncology outpatient.

The patient was readmitted within one week of discharge with a new complaint of worsening dysphagia. As ultrasound has been previously performed, CT of the neck was ordered and revealed extensive bilateral cervical, supraclavicular and mediastinal lymphadenopathy. There was also re-visualization of the right thyroid mass and diffuse lytic lesions throughout the cervical spinal skull base suggestive of osseous metastasis (Fig. 4). He underwent fluoroscopic modified barium swallow which showed aspiration of all liquids. The patient demonstrated poor pharyngeal motility with pronounced weakness on the right side and reduced epiglottic inversion with moderate pharyngeal residue (Fig. 5). It was suspected that his dysphagia was due to right-sided cranial nerve impairment with near absent right pharyngeal contraction and suspected incomplete glottic closure. His liver function declined acutely during his admission and he developed hepatorenal syndrome and lactic acidosis. He was transferred to the intensive care unit on hospital day 9 for hypotension and hemodynamic instability. After interdisciplinary discussions and goals of care with family and patient, he was ultimately discharged with hospice care.

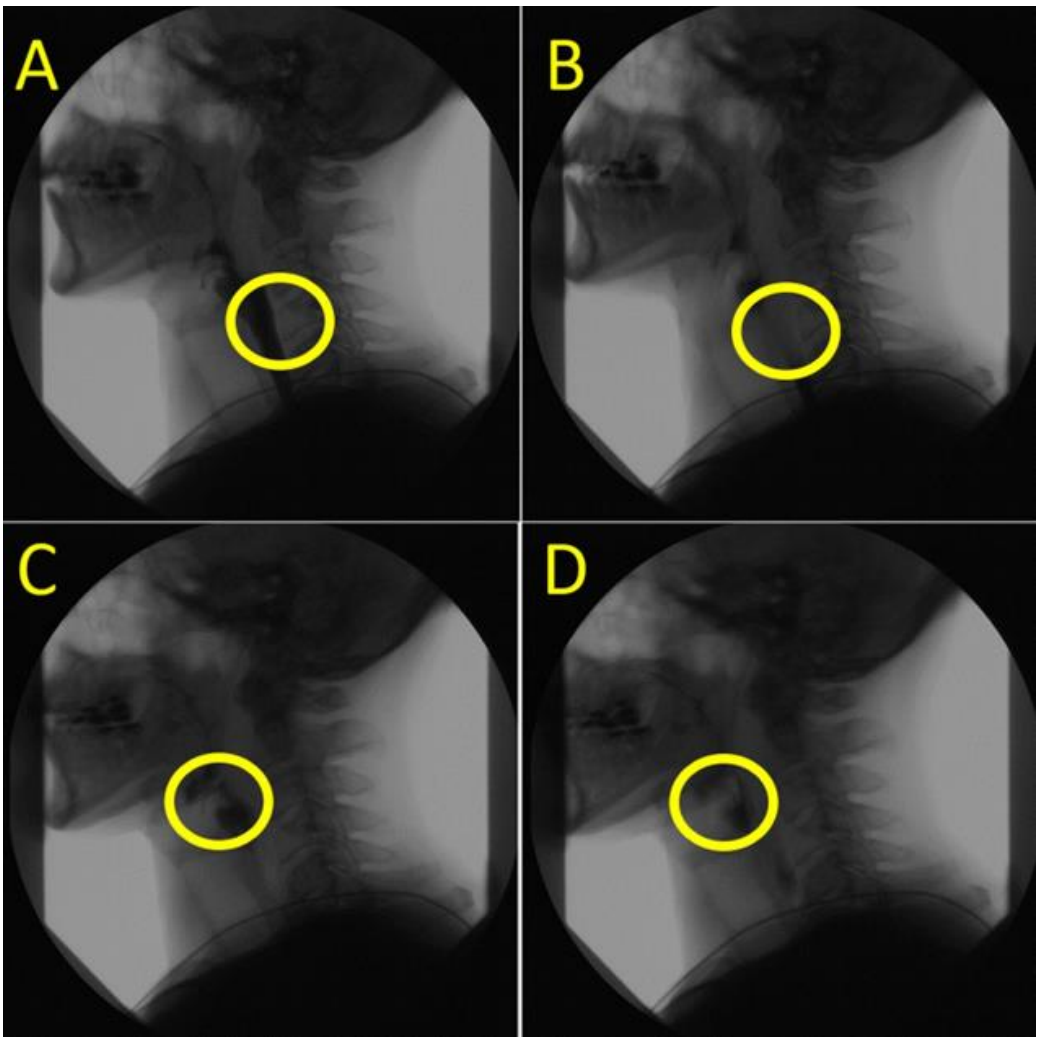

Figure 1: Computed Tomography (CT) of the abdomen and pelvis. (A): A mass of the left liver lobe measuring 3.6 x 3.4 cm (yellow circle) with hypodense lesion of the posterior right liver lobe measuring 5.9 x 4.6 (red circle); (B): Pathologic lymphadenopathy with the largest lymph node measuring 4.4 x 4.1 cm (yellow arrow); (C and D) innumerable metastatic lesions of the bone with the largest lesion of the T8 vertebral body measuring 1.6 x 1.4 cm (red arrows).
Further work up of new neck mass was pursed with an ultrasound that revealed multiple mor-phologically abnormal lesions in the right-side level 2, 3 and 4 lymph nodes. The right thyroid lobe appeared to be replaced by a heterogenous mass measuring 5.3 cm in the maximal dimen-sion. The left thyroid appeared normal (B).

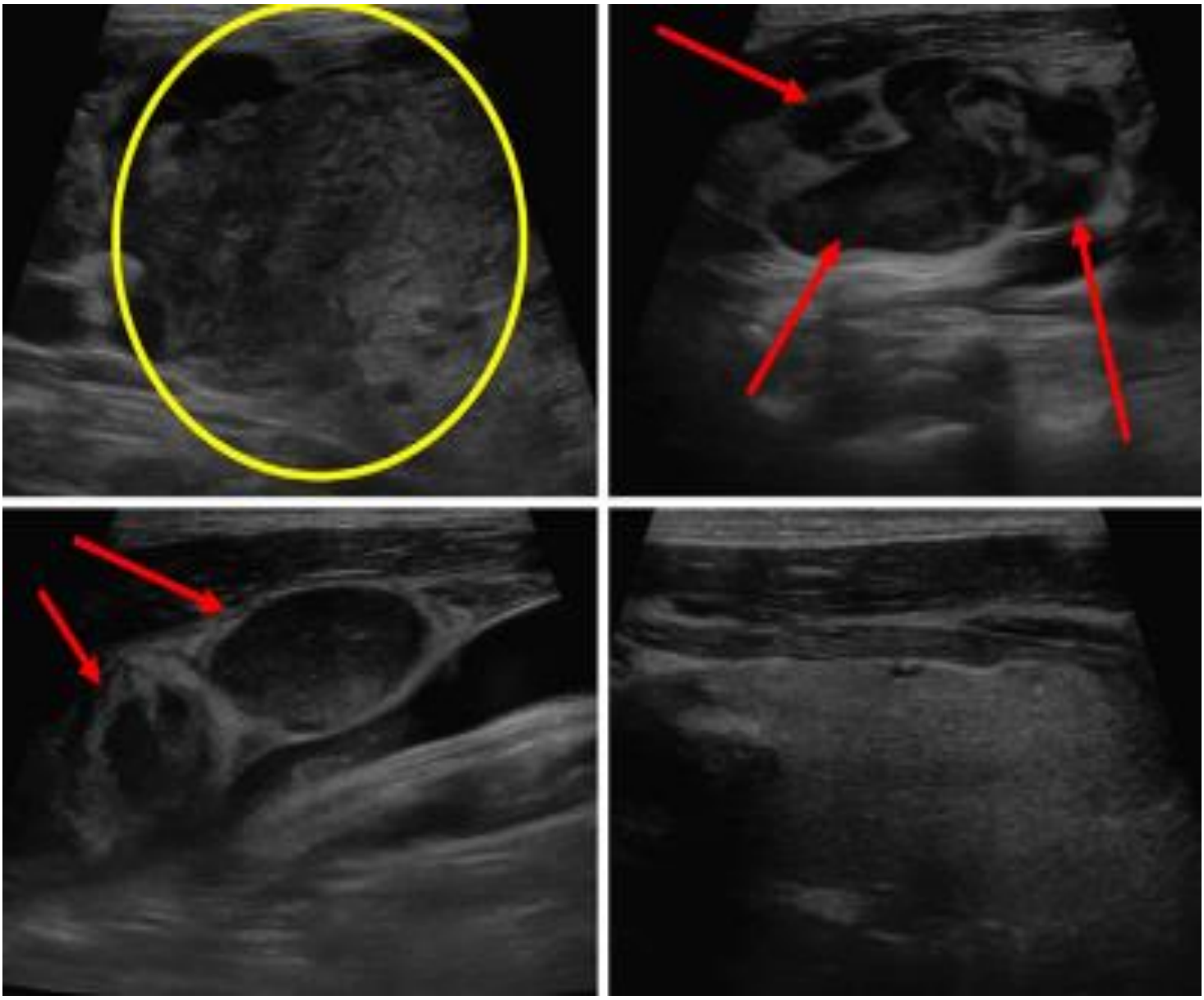

Figure 2: Ultrasound of the neck, long-axis view. (a): Right lobe of thyroid with heterogenous mass (yellow circle); (b): Morphologically abnormal lesions in the level 3 lymph nodes of the right side of the neck (red arrows); (c): Morphologically abnormal lesions of level 3 and level 4 lymph nodes on the right side of the neck (red arrows); (d): Normal appearance of the left thy-roid lobe.

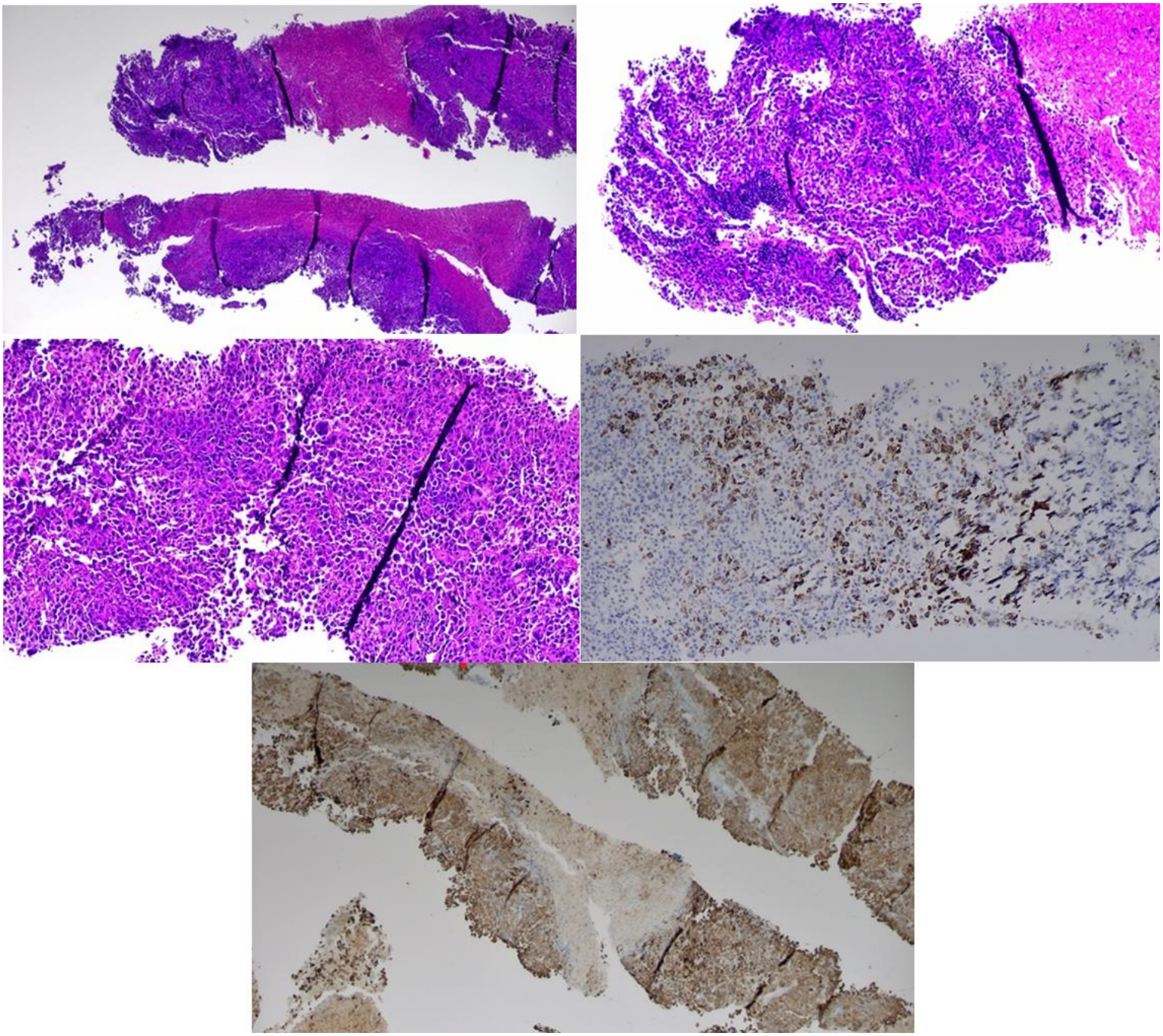

Figure 3: Pathology slide of right lymph node biopsy. Hepatocellular carcinoma was confirmed by the tumor cells staining positive for PAN-K, Glypican-3, HepPar1 and anti-arginase and nega-tive for p40 and CEA-poly. (a): HandE stain at 40x magnification; (b): HandE stain at 100x magnification; (c): HandE stain at 200x magnification; (d): HEPPAR1 stain; (e): 3e. PAN-keratin stain.

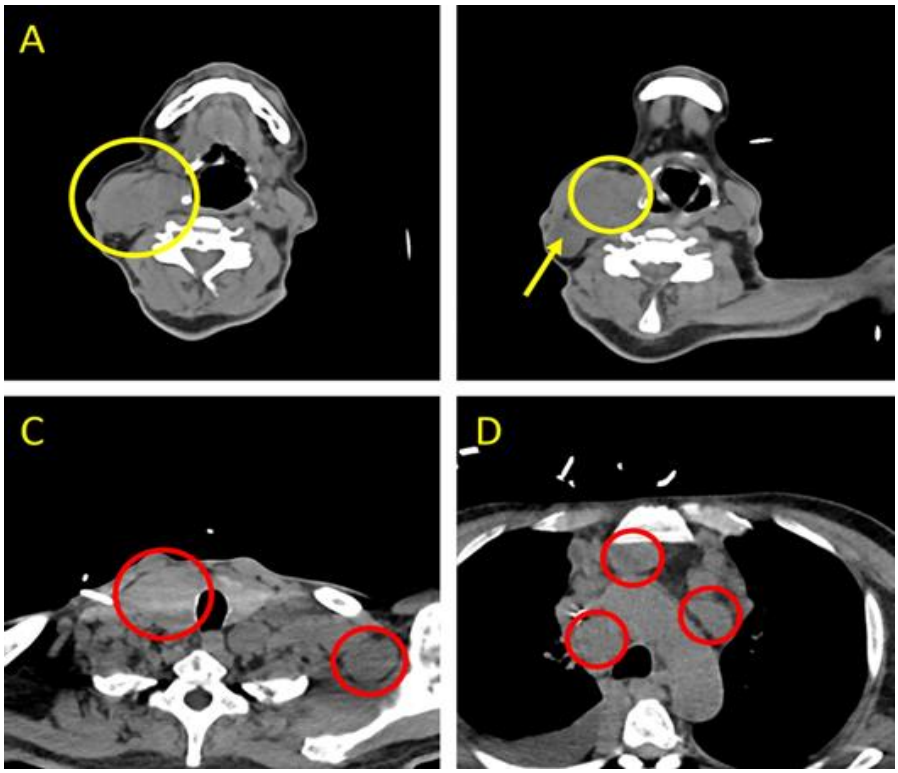

Figure 4: Computed Tomography (CT) of the neck. (a-b) Mass of the right thyroid measuring 4.3 cm x 3.7 cm x 5.1 cm (yellow circles) and cervical lymphadenopathy (yellow arrow). (c-d) Exten-sive mediastinal lymphadenopathy (red circles).

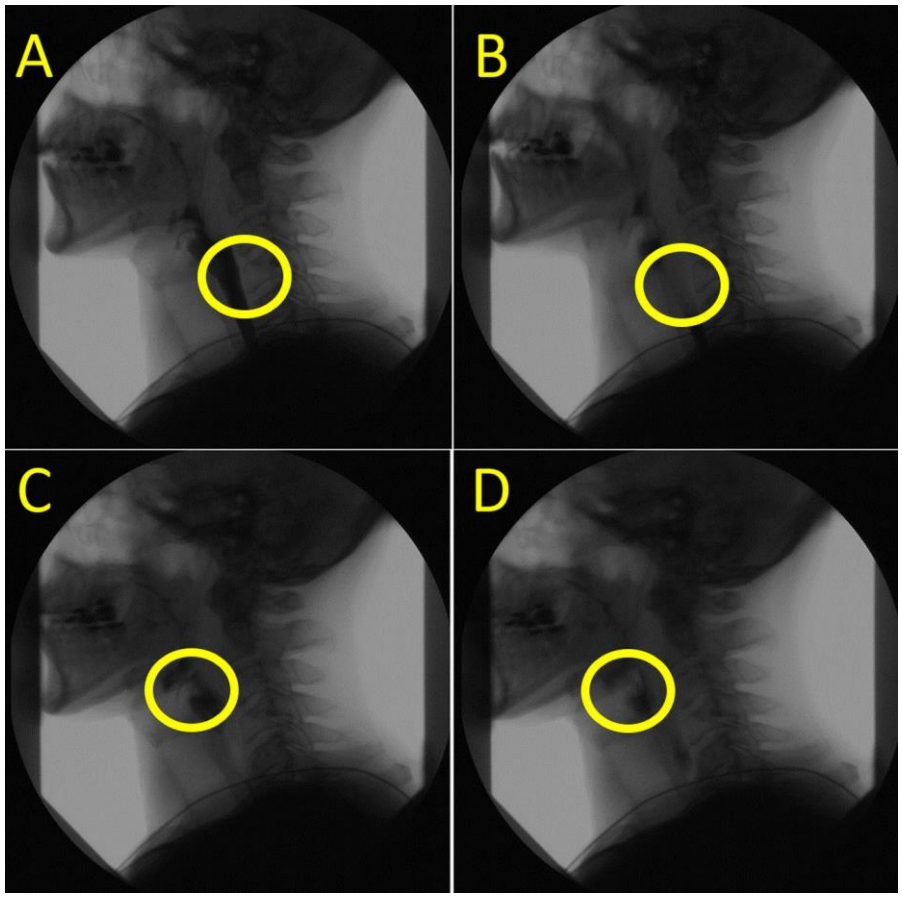

Figure 5: Fluoroscopic Modified Barium Swallow (MBS). (a-d) The honey-thick liquid series is shown. There is aspiration of the liquid during the swallowing phase. Moderate pharyngeal residue can be seen (yellow circle).

Discussion

This case highlights the rare event of hepatocellular carcinoma with metastasis to the thyroid gland and the diagnostic and treatment challenges associated with such a devastating diagnosis. Metastatic cancer to the thyroid gland generally is considered a poor prognostic factor, with patients expiring shortly after the diagnosis [14,15]. This rapid mortality following diagnosis may contribute to the low prevalence of patients with thyroid metastasis [16]. It is challenging to obtain exact estimates of this condition's prevalence, but studies have shown variable prevalence of metastatic cancer to the thyroid, ranging from 1.9% to 24% [16]. Interestingly, up to 3% of patients who undergo surgery for thyroid malignancy have metastatic disease and not a pri-mary thyroid neoplasm [16]. The most common cancer metastasizing to the thyroid gland is renal cell carcinoma, accounting for almost half of the cases; other common primary malignancies include melanomas, sarcomas, lung, colorectal, breast and head and neck carcinomas [14,16,17]. Metastatic cancer to the thyroid gland can present with symptoms of transient thyrotoxicosis, compression, airway obstruction, dysphagia and hoarseness [11]. In this case, the patient developed dysphagia shortly after the diagnosis thyroid metastasis. Some patients are asymptomatic and lesions are detected incidentally or during autopsy [16,17]. Metastasis to the thyroid from HCC is rare, but physicians should have a high index of suspicion for thyroid metastasis when presented with new findings that could indicate thyroid involvement in patients with a history of HCC, as in this case [16].

The incidence of extrahepatic metastasis in HCC has been reported to range from 15% to 17%, with vascular invasion considered as a dominant factor [18]. However, in addition to hematogenous spread, HCC can metastasize via direct tumor invasion and the lymphatic system [5]. Most of the lymphatic spread reported in HCC is to local lymph nodes from lymphatic vessels that drain the tumor [19]. In addition, metastasis to Virchow-Troisier's left supraclavicular lymph node is well characterized as it follows similar lymph drainage to the stomach, which more commonly metastasizes to this area [19]. Given our patient's significant right cervical lymphadenopathy, it is difficult to determine the exact mechanism or if both hematogenous and lym-phogenous dissemination occurred concomitantly to the cervical lymph nodes and the thyroid. Only a few cases in the literature have reported metastatic HCC to the right cervical lymph nodes [19]. Considering the normal lymphatic flow from the liver, it is not an expected site for distant metastasis. Some authors have described the possibility of lymphangiogenesis, new lymphatic vessel formation, driven by vascular endothelial growth factor C produced by the car-cinoma, that generates bypasses to the normal lymph flow [20]. In contrast, others have de-scribed anatomical variants that may explain this occurrence in conjunction with the disor-ganized architecture of the cirrhotic liver that alters lymph production and drainage [19]. We confirmed that the right cervical lymph nodes were positive for HCC using ultrasound-guided core biopsy of a lymph node and the disease burden was more significant in the lymph nodes than in the thyroid gland based on imaging studies. Therefore, even though we cannot rule out the possibility of hematogenous spread to the gland, it is certainly possible that the disease initially metastasized through the lymphatic system and then spread to the thyroid gland. Other authors have proposed this mechanism of HCC to thyroid metastasis; Liang, et al., confirmed thyroid metastasis from HCC using Fine Needle Aspiration (FNA) in a patient with cervical lym-phadenopathy appearing concurrently with the thyroid findings [12]. Few cases of HCC with metastasis to the thyroid have been previously reported in medical literature [7-13]. Each case is detailed in Table 1.

Each of the above cases confirmed the diagnosis of HCC with metastasis to the thyroid through either biopsy or surgical resection of the thyroid tissue [7-13]. This was deemed not possible in our patient due to the advanced stage of his disease and the concern for airway compromise due to hemorrhage as a result of the procedure. Furthermore, it was noted that 3 patients opt-ed to undergo further therapy and subsequently had no further tumor recurrence [8,10,11]. Unfortunately, due to our patient's rapidly worsening condition, it was determined that there were no further therapies available to him, thus necessitating a conversation about transition-ing to hospice care. Also of interest, all previously reported cases of thyroid metastasis found in our review of literature occurred either bilaterally or on the left side of the thyroid [7-13]. However, our patient's thyroid metastasis manifested on the right thyroid lobe. A possible ex-planation for this phenomenon is lymphatic flow from the liver leading to drainage into the thoracic duct, which typically terminates on the left side of the body [21]. However, the thoracic duct has been shown to terminate on the right side in 2-3% of cases and bilaterally in 1.5% of cases [21]. As discussed previously in this paper, it is possible that the disease metastasized through the lymphatic system thus making it entirely possible that our patient was one of the rare 2-3% of cases where his thoracic duct terminated on the right side of his body, thus allow-ing his disease to metastasize to his right thyroid lobe and cervical lymph nodes. Therefore, our patient's case is, to our knowledge, the first reported case of HCC with metastasis to only the right lobe of the thyroid.

This case report has some limitations. This is a report of HCC with metastasis to the thyroid in a single patient, thus limiting the

generalizability of our findings. In addition, it was decided that the patient's biopsy would be taken from one of his cervical lymph nodes rather than the thy-roid mass itself out of abundant concern for the patient's safety. However, because of this decision, we cannot rule out the possibility that the thyroid mass is a primary cancer of thyroid origin with findings of metastatic HCC in the cervical lymph nodes. However, when considering the proximity of the lymph nodes to the thyroid mass, we believe that it is much more likely that the thyroid mass was in fact metastatic HCC.

It is an extremely rare and unfortunate event for HCC to metastasize to the thyroid. If a new thyroid mass or enlarged cervical lymph node is discovered, it is vital to establish if these new findings are due to a primary thyroid malignancy or HCC metastasis. Just like with our patient, FNA of either the thyroid gland or a cervical lymph node could greatly assist in these diagnostics efforts. Per National Comprehensive Cancer Network (NCCN) guidelines, first-line systemic therapy for metastatic HCC is palliative immunotherapy with atezolizumab and bevacizumab, the same regimen our patient was to start prior to the discovery of the thyroid metastasis [22]. However, decisions on treatment should be made after extensive discussion with the patient. As demonstrated in this case, diagnosis of thyroid metastasis in HCC is often accompanied by poor prognosis and rapid decline [14,15]. Treatment may not be feasible for some patients depending on age, functional ability and overall progression of disease.

Authors	Reference	Year	Patient Demographics	Presentation	Laterality of Thyroid Mass	Diagnosis Confirmation	Outcome
Tunca, et al.,	13	2006	71-year-old male	Rapidly enlarging neck mass and dysphagia	Left	Core needle biopsy of thyroid mass	Scheduled to start chemotherapy
Liang, et al.,	12	2007	54-year-old male	New-onset dyspnea and several neck nodules	Left	Fine needle aspiration and cytology of thyroid mass	Total thyroidectomy with bilateral regional lymph node dissection; passed 8 months later due to recurrent HCC complicated by sepsis
Toshima, et al.,	11	2010	74-year-old male	Asymptomatic with left lobe of thyroid tumor seen on screening imaging	Left	Fine needle aspiration and cytology of thyroid mass	Thyroidectomy of left lobe with regional lymph node dissection; has undergone radiation therapy with no further distant metastasis
Silva, et al.,	10	2013	62-year-old female	Dysphagia and enlarged neck	Bilateral	Fine needle aspiration and total thyroidectomy pathology	Liver resection and total thyroidectomy with no tumor recurrence
Kim, et al.,	9	2015	53-year-old male	Multiple masses of left anterior and lateral neck and left internal jugular chain	Left	US-guided core needle biopsy of left thyroid mass and left level 3 lymph node	Passed 20 days after diagnosis due to hepatorenal syndrome
Yin, et al.,	8	2018	41-year-old male	Left neck mass after hepatolobectomy	Left	Left thyroidectomy	Alive post-thyroidectomy

Park, et al.,	7	2019	63-year-old male	New palpable left upper anterior neck mass and change of voice	Left	US-guided core needle biopsy of left thyroid mass	Radiation therapy
Current case		2023	51-year-old male	Neck mass and dysphagia	Right	Biopsy of right-sided cervical lymph node	Opted for home with hospice

Table 1: Details of previously reported cases of hepatocellular carcinoma with thyroid metastasis.

Conclusion

Hepatocellular carcinoma can very rarely metastasize to the thyroid and is associated with poor overall prognosis. Patients should be adequately counseled on the prognosis and the treatment options available including palliative measures. It is vital physicians be aware of the potential for HCC to spread to the thyroid and have a high index of suspicion to investigate when evaluating a patient with symptoms of dysphagia or signs of cervical mass and hypercalcemia. A thorough assessment is important for early detection of HCC metastasis to improve patient outcomes and clinical practices. Increased recognition of HCC thyroid metastasis is crucial to expand the data and literature currently available.

Conflict of Interests

The authors declare no conflict of interest regarding authorship roles or publication of article.

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Authors Contribution

All the authors have equal contribution and all the authors have read and agreed to the published version of the manuscript.

Data Availability

Not applicable

Consent for Publication

Not applicable

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