Case report

Metastatic basaloid squamous cell carcinoma of thymic origin

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SUMMARY

A 57-year-old man with a known anterior mediastinal mass presented with abdominal distension, jaundice, and signs of urinary and bowel obstruction. Labs revealed leukocytosis, transaminitis, direct hyperbilirubinaemia and elevated levels of alkaline phosphatase, lactate dehydrogenase and uric acid. Subsequent imaging revealed the anterior mediastinal mass and diffuse liver lesions consistent with metastatic disease. MRI of the spine and brain were negative for metastases. Liver biopsy and immunohistochemistry revealed basaloid squamous cell carcinoma of thymic origin. Treatment with capecitabine was initiated but was complicated by worsening liver and kidney failure. Eventually, due to continued worsening of the patient's condition and minimal treatment response, capecitabine was stopped during cycle 1 and the patient was discharged to inpatient hospice with comfort care. In this case report, we highlight the presenting features, imaging findings and management of a patient with metastatic thymic carcinoma.

BACKGROUND

Thymic carcinoma is a rare form of thymic malignancy, with basaloid squamous cell carcinoma as a subtype with fewer than 30 cases reported in the literature.¹ We report the second case of thymic basaloid squamous cell carcinoma with liver metastases.

CASE PRESENTATION

A 57-year-old man initially presented in May 2018 to an outpatient clinic for progressively worsening neck pain of 5 years' duration with associated C6-C7 radiculopathy of the right arm. His medical history included gout and hyperlipidaemia, with a family history notable for coronary artery disease. He had a normal colonoscopy at the age of 53. Review of systems and physical examination were unremarkable at this time.

One month later, a cervical spine X-ray revealed non-specific widening of the mediastinum. Follow-up CT scan after 2 months noted cervical stenosis in addition to a 7.8×7.7×4.2 cm anterior mediastinal mass. Within 3 months, the patient became symptomatic with right-sided superior chest wall pain, worse with inspiration and when lying prone. Cardiothoracic surgery was evaluating the patient for outpatient resection of the mass pending MRI of the abdomen, chest and spine.

On the day prior to his MRI (4 months from initial presentation), the patient presented to an ambulatory clinic with 1 week of suprapubic pain with urinary retention, dark orange urine output, pale stools and constipation with intermittent diarrhoeal episodes. He also had chills, cold sweats, nausea and progressive jaundice with scleral icterus. On physical examination, his abdomen was tense, distended and diffusely tender to palpation. His liver edge was firm and palpable 2 cm below the costal margin. There were no palpable masses or cervical, axillary or inguinal lymphadenopathy. His overall clinical picture prompted hospital admission.

INVESTIGATIONS

Initial laboratory abnormalities were significant for WBC of 15 400 cells/μL, total bilirubin of 6.8 mg/dL, aspartate aminotransferase of 366 IU/L, alanine transaminase of 167 IU/L, alkaline phosphatase of 464 IU/L and creatinine of 1.6 mg/dL (table 1). He also had elevations in carcinoembryonic antigen (CEA) at 322 ng/mL, lactate dehydrogenase (LDH) at 1382 U/L, uric acid at 9.1 mg/dL and lactic acid at 4.8 mmol/L. His Model for End-Stage Liver Disease (MELD) score on admission was 22.

CT chest and abdomen showed enlargement of his anterior mediastinal mass, now 8.5×4.5 cm, with punctate internal calcification, ill-defined margins, central hypodensity which likely represented necrosis and early local invasion into the right manubrium (figure 1). On follow-up MRI, there were additional diffuse liver lesions concerning for metastatic disease (figures 2A–C) along with 15 cm splenomegaly. Positron emission tomography-CT (PET/CT) demonstrated that the lesion had avid fluorodeoxyglucose (FDG) uptake, with a maximum standardised uptake value (SUV) of 14.6. There was also diffuse tracer uptake throughout both the right and left hepatic lobes with representative SUV maximum of 16.5. Finally, there was a small number of ascites layering in the pelvis which demonstrated mild FDG avidity, with a maximum SUV of 2.6.

A liver biopsy was performed which revealed basaloid squamous cell carcinoma of thymic origin (figure 3). The tumour cells were positive for P63, CD5 (figure 4), CD117 and PAX8 and negative for synaptophysin, chromogranin, napsin and TTF-1, and CK20.

DIFFERENTIAL DIAGNOSIS

Thymoma, lymphoma, germ cell tumour, ectopic thyroid gland and thymic carcinoma.

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Table 1 Laboratory results during hospital course

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
BUN (mg/dL)	20	20	24	34	38	41	45	48	54	63	75	88	98	114
Creatinine (mg/dL)	1.1	1.2	1.4	1.6	1.6	1.6	1.5	1.5	1.6	2	2.2	2.2	2.6	3.2
Total protein (g/dL)	6.8	6.1	6.4	6.3	5.9	5.6	5.4	5.2	5.2	4.9	4.8	4.8	4.8	5.2
Albumin (g/dL)	3.7	3.3	3.3	3.4	3.3	3.1	3.2	3.1	3.2	2.8	2.7	2.7	3.4	3.9
Total bilirubin (mg/dL)	6.8	6.9	7.4	8.2	9	9.5	12.4	12.5	13.2	14	15.5	16.9	16.8	17.4
Direct bilirubin (mg/dL)	–	5.6	–	–	–	–	10.3	10.3	10.7	10.9	12.3	13.7	13.5	13.9
Alkaline phosphatase (IU/L)	464	421	434	398	358	323	317	323	319	316	305	286	225	184
AST (IU/L)	366	358	432	458	503	474	542	724	869	860	798	694	450	316
ALT (IU/L)	167	161	186	195	201	190	209	275	342	350	337	288	200	149
White blood cells (cells/ μ L)	15.4	14.2	15.3	17.7	19.9	17.9	18.2	19	25.7	27.1	27.7	28.2	21.8	15.5
Haemoglobin (g/dL)	13.6	13.4	13.5	12.3	11.9	11.3	11.2	11	11.2	10.9	10.8	10.3	8.7	8
Haematocrit (%)	40.7	39.2	40.1	36.9	35	33.6	34	33.5	33.2	32.3	31.7	29.5	25.4	22.8
Platelets ($10^3/\mu$ L)	180	183	181	176	154	120	162	164	153	133	141	124	103	112
Prothrombin time (seconds)	15.9	–	–	–	–	18.7	21.6	24.6	30.3	36	33.8	33.1	34.5	34.9
INR	1.2	–	–	–	–	1.5	1.8	2.2	2.8	3.6	3.3	3.2	3.4	3.4
LDH (U/L)	–	1382	–	1470	–	1357	1657	1896	1872	1728	1855	1666	1345	1112
Uric acid (mg/dL)	–	9.1	–	9.1	7.9	5.1	4.4	4.1	–	3.7	3.6	3.6	3.7	4.1
MELD Score	22	–	–	–	–	28	28	30	34	38	39	39	40	40

The bold values show important numerical trends in the disease progression. Meanwhile, the other non-bolded values were included to provide additional context that is important for a comprehensive understanding of the case.

ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; INR, international normalised ratio; LDH, lactate dehydrogenase; MELD, Model for End-Stage Liver Disease.

TREATMENT

The patient was initially treated with allopurinol and intravenous fluids due to concerns of spontaneous tumour lysis syndrome given his elevated LDH, uric acid and creatinine on admission. He was also treated for suspected acute cholangitis with vancomycin, cefepime and metronidazole. Gastroenterology (GI) was consulted for potential intervention to relieve biliary obstruction. However, due to the absence of intrahepatic biliary congestion and common bile duct dilation, no GI intervention was performed. Additionally, despite the patient's clinical signs of bowel obstruction, CT scan of the abdomen was unremarkable.

During the hospital course, the patient experienced a progressive decline in hepatic function, with increasing total/direct bilirubin, LDH, prothrombin time and international normalized ratio (INR), and decreasing albumin (table 1). He also developed severe hepatic encephalopathy. Treatment with lactulose was

initiated, which relieved the patient's constipation and temporarily restored mentation before the patient's encephalopathy returned. Rifaximin was initiated but also failed to improve the patient's confusion.

Liver biopsy pathology results returned on hospital day 9, and oncology recommended prompt chemotherapy. Capecitabine 1000 mg twice daily was initiated with the intention to treat for 14 days on a 21-day cycle. Although dual-agent chemotherapy regimens are preferred for treating thymic carcinomas, especially squamous cell cancers, his acute liver failure and renal failure limited the use of multiple chemotherapeutic agents.

OUTCOME AND FOLLOW-UP

The patient developed hepatorenal syndrome which worsened despite initiation of octreotide, midodrine and albumin. His laboratory values peaked at a total bilirubin of 17.4 mg/dL, direct bilirubin of 13.9 mg/dL, albumin of 2.7 g/dL, INR of 3.4, blood urea nitrogen of 114 mg/dL, and creatinine of 3.2 mg/dL (table 1). His MELD score at this time was 40. Given the likely futility of treatment, goals of care were addressed with the family who chose to discontinue capecitabine on day 6. The patient was transitioned to inpatient hospice care and succumbed to his disease 2 days after discharge.

DISCUSSION

Few case reports are present in the literature that describe the natural history of disease and treatment guidelines for thymic basaloid squamous cell carcinoma.¹ This cancer shows predominance in middle-aged to elderly patients.¹ Case reports have shown tumours that ranged from 4.4 to 17 cm at initial diagnosis and have presented either as incidental radiographic findings on X-ray or with dyspnoea on exertion.¹ Level of aggression of this subtype of thymic carcinoma is varied; previously, it was thought to be a low-grade neoplasm, but studies have shown aggressive behaviour in about 30% of cases.² Clinical information is available for 22 of 29 reported cases in the literature, with 8 cases

Figure 1 CT demonstrating 8.5×4.5 cm mass in the anterior mediastinum with punctate internal calcification, ill-defined margins and central hypodensity likely representing necrosis, and early local invasion into the manubrium.

Figure 2 (A) CT non-contrast revealing hypodensities in the liver. (B) MRI T2 axial sequence demonstrating diffuse hyperintense signals throughout the liver (yellow arrows). (C) MRI T2 coronal sequence demonstrating diffuse hyperintense signals throughout the liver (yellow arrows).

describing the development of metastases.¹ Six of the 22 patients eventually died from their disease, 5 of whom had metastatic disease.¹ Local invasion to the lung, pleura, bone, vasculature and

Figure 3 H&E-stained sections of core biopsy demonstrating basaloid nests of carcinoma cells infiltrating hepatic parenchyma. (A) 20× magnification; (B) 40× magnification; (C) 200× magnification; (D) 400× magnification .

intrathoracic and cervical lymph nodes have been reported.^{1–3} Only one case described metastatic liver involvement.⁴ There is also a case report that described an intrahepatic tumour consistent with basaloid squamous cell carcinoma but of unknown

Figure 4 Immunohistochemical studies. (A) CD5 highlighting carcinoma cells. (B) CD117 (C-Kit) showing reactivity within tumour cells. (C) p63 highlighting carcinoma cells. (D) Cytokeratin 7 showing no significant expression within tumour cells but highlights background bile ductules within hepatic parenchyma.

primary origin.⁵ It is important to highlight that the liver biopsy in our case clearly identified the tumour and source of origin, playing a key role in guiding management.

Treatment recommendations for thymic basaloid squamous cell carcinomas are unclear. One study examining 17 of those case reports noted that all individuals underwent surgical resection of their anterior mediastinal mass.¹ Six of those patients also underwent radiation to the mediastinum, with one patient undergoing additional radiation to their metastasis within the lung.¹ Of four patients with metastatic disease, two received systemic chemotherapy, one died intraoperatively and one had surgical resection of liver metastases.¹⁴ Chemotherapy agents for one of the cases consisted of neoadjuvant cisplatin/adriamycin.⁶

Notably, the patient who developed a metastatic disease to the liver underwent surgical resection of her primary thymic basaloid squamous cell carcinoma followed by partial hepatectomy. One year later, there was a recurrent lesion in the liver which was again resected successfully. She underwent concurrent radiation therapy and had no evidence of disease recurrence at 7 months.⁴ Meanwhile, the patient with the intrahepatic basaloid squamous cell carcinoma of unknown origin underwent a hemihepatectomy for a 27×25×15 cm centrally necrotic tumour, and she died 2 years later after several intra-abdominal recurrences.⁵

Although surgical resection of the primary thymic tumour was the most widely used approach, the use of chemotherapeutics was varied and rare. A recent study, on which our treatment plan was based, demonstrated some success in treating metastatic thymic epithelial neoplasms with capecitabine 1000 mg/m² two times per day and celecoxib 200 mg two times per day for 14 days on a 21-day cycle. Three patients in that study had thymic carcinomas, of which two had a complete response to therapy and one had a partial response.⁷

Although capecitabine has been shown to cause elevations in serum aminotransferases and bilirubin, it has not been shown to cause clinically apparent hepatocellular and/or cholestatic liver injury like celecoxib.^{8,9} Due to innumerable liver metastases in our patient, monotherapy with capecitabine was initiated to prevent the adverse effects from celecoxib. However, in addition to the widespread liver metastases, our patient also had growth of the primary tumour from 7.9×3.8 to 8.5×4.5 cm within 4 days prior to initiation of chemotherapy. As such, it is likely that his poor response to capecitabine was likely a result of aggressive disease progression rather than a direct complication of capecitabine.

Learning points

- ▶ Thymic basaloid squamous cell carcinoma has the potential to spread to the liver. Biopsies of suspected sites of metastasis are critical in guiding diagnosis and treatment with potentially hepatotoxic drugs.
- ▶ Basaloid squamous cell carcinoma can cause diffuse metastatic liver involvement leading to acute liver failure and hepatorenal syndrome.
- ▶ Surgical resection of the thymic neoplasm is preferred; however, capecitabine and celecoxib may have utility in patients with thymic neoplasms.
- ▶ Early detection and diagnosis of basaloid squamous cell carcinoma may reduce mortality and morbidity.

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