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CASE REPORT

Medullary thyroid cancer and pseudocirrhosis: case report and literature review

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ABSTRACT

Pseudocirrhosis is a rare form of liver disease that can cause clinical symptoms and radiographic signs of cirrhosis; however, its histologic features suggest a distinct pathologic process. In the setting of cancer, hepatic metastases and systemic chemotherapy are suspected causes of pseudocirrhosis. Here, we present a patient with medullary thyroid carcinoma metastatic to the liver who developed pseudocirrhosis while on maintenance sunitinib after receiving 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) in combination with sunitinib. Cirrhotic change in liver morphology was accompanied by diffusely infiltrative carcinomatous disease resembling the primary tumor. We discuss the diagnosis of pseudocirrhosis in this case and review the literature regarding pseudocirrhosis in cancer.

KEY WORDS

Medullary thyroid cancer, pseudocirrhosis, carcinomatous cirrhosis

1. CASE DESCRIPTION

A 49-year-old white woman presented in January 2008 with a left-sided cervical mass without associated complaints of neck pain, stridor, dysphonia, dysphagia, malaise, fever, or chills. Physical examination was remarkable for a firm, mildly tender 4-cm anterior cervical lymph node.

Vital signs and initial laboratory tests, including a complete blood count, comprehensive metabolic panel, thyroid-stimulating hormone, and free T_4, were within normal limits. Computed tomography (CT) imaging of the neck demonstrated right thyroid lobe enlargement, multiple heterogeneous masses in the left thyroid lobe, and multifocal local and regional lymphadenopathy. Fine-needle aspiration of the dominant thyroid mass revealed highly proliferative calcitonin-positive cells with epithelioid and spindle-cell morphologies, and a diagnosis of medullary thyroid carcinoma (MTC) was made.

On baseline positron-emission tomography (PET)/CT imaging, hypodensities corresponding to hypermetabolic foci in both hepatic lobes were observed [Figure 1(A)]. Biopsies of these regions showed poorly differentiated epithelioid cells positive for calcitonin [Figure 1(B)], thyroid transcription factor 1 [Figure 1(C)], and cytokeratin 7, but negative for thyroglobulin, cytokeratin 20, and alpha-fetoprotein, which is consistent with MTC metastatic to the liver. At the time of diagnosis, the patient was not taking medications, and she had an unremarkable personal medical history and no family history of thyroid disease, endocrine disorders, or neoplasm.

In March 2008, the patient enrolled in a phase I clinical trial (NCT00599924) of 5-fluorouracil (5FU), leucovorin, and oxaliplatin (FOLFOX) in combination with sunitinib, a tyrosine kinase inhibitor with multiple targets, including the vascular endothelial growth factor receptor and the rearranged during transfection (*RET*) proto-oncogene, which is often upregulated in neuroendocrine tumors such as MTC [1]. The patient received FOLFOX (leucovorin 400 mg/m^2; 5-fluorouracil 400 mg/m^2 intravenous bolus, followed by 2400 mg/m^2 infusion over 46 hours; oxaliplatin 85 mg/m^2) every 2 weeks and sunitinib 37.5 g daily for 4 weeks, followed by a 2-week rest period. In July 2008, after 4 months of FOLFOX–sunitinib, the patient showed measureable tumor regression in the liver [Figure 1(D)] that qualified as a partial response according to the Response Evaluation Criteria in Solid Tumors. The FOLFOX was discontinued, and the patient was maintained on single-agent sunitinib, which she tolerated well for 15 months with stable liver metastases. The patient underwent serial PET/CT imaging without intravenous contrast to monitor her disease.

In November 2009 (21 months after diagnosis), the patient developed abdominal bloating, early satiety, and right upper quadrant pain that increased with inspiration. Pulmonary exam demonstrated dullness

to percussion and decreased breath sounds at the right lung base. Abdominal distension was noted without rebounding, guarding, or tenderness to percussion.

A comprehensive metabolic panel revealed normal values, with the exception of decreased albumin and elevated aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and international normalized ratio (Table I). Imaging (CT with intravenous contrast) demonstrated a nodular contour of the liver [Figure 1(F), closed arrowhead] with capsular retraction [Figure 1(F), open arrowhead], mild ascites, and right-sided pleural effusion that was not previously present [Figure 1(G), closed arrowhead, compared with Figure 1(E)]. Thoracentesis revealed no evidence of malignancy or infection in the effusion.

The patient had no history of alcohol or intravenous drug use, and laboratory testing for causes of liver disease, including hepatitis B and C serologies, autoimmune serologies, iron studies, and α1-antitrypsin levels, were all negative or normal. Based on clinical evidence of portal hypertension, the patient underwent upper endoscopy, which revealed esophageal varices and portal hypertensive gastropathy.

To determine the nature of the liver disease, transjugular liver biopsy with transhepatic pressure measurements was performed. The transhepatic pressure gradient confirmed portal hypertension [37 mmHg (normal: <5 mmHg)] and transjugular liver biopsy revealed sheets and nests of infiltrative epithelioid and spindle cells with a prominent fibrotic stromal response [Figure 2(A,B)], which was occasionally accompanied by desmoplasia [Figure 2(C)]. The background hepatic plate architecture was intact, with alternating portal tracts [Figure 2(D), closed arrowhead] and central veins [Figure 2(D), open arrowhead] at normally spaced intervals, without hepatocyte atrophy or inflammation. Septal fibrosis typical of advanced liver disease was not observed. The histologic features of the liver suggested that metastatic MTC was responsible for the cirrhotic changes in the liver and the portal hypertension, which is consistent with a diagnosis of pseudocirrhosis, also known as carcinomatous cirrhosis.

This result was considered to represent disease progression, and sunitinib was discontinued in December 2009. The patient began a trial of sorafenib in February 2010 at a starting dose of 200 mg, which was gradually increased to 400 mg twice

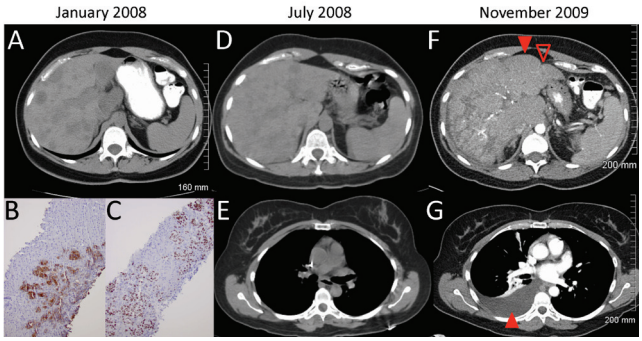

FIGURE 1 In January 2008, (A) abdominal computed tomography (CT) scan demonstrated hepatic hypodensities, and biopsy of a liver lesion was positive for (B) calcitonin and (C) thyroid transcription factor 1, confirming the diagnosis of metastatic medullary thyroid cancer. In July 2008, FOLFOX chemotherapy (5-fluorouracil–leucovorin–oxaliplatin) was discontinued, and the patient was maintained on sunitinib after (D) tumor regression. In November 2009, CT imaging after complaints of abdominal bloating, early satiety, and right upper quadrant pain demonstrated (F) a cirrhotic-appearing liver with a nodular surface (closed arrowhead) and capsular retraction (open arrowhead). The patient also developed (B) a pleural effusion (arrowhead) that was not present on earlier imaging (E).

TABLE I Laboratory values at baseline and in November 2009, when symptoms of progressive disease developed

Test	*Normal range*	*At baseline*	*At disease progression*
AST (U/L)	0–47	28	108
ALT (U/L)	0–47	32	95
ALP (U/L)	39–117	58	405
Albumin (g/dL)	3.4–5.0	3.8	3.1
INR	0.9–1.1	1.1	1.2

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; INR = international normalized ratio.

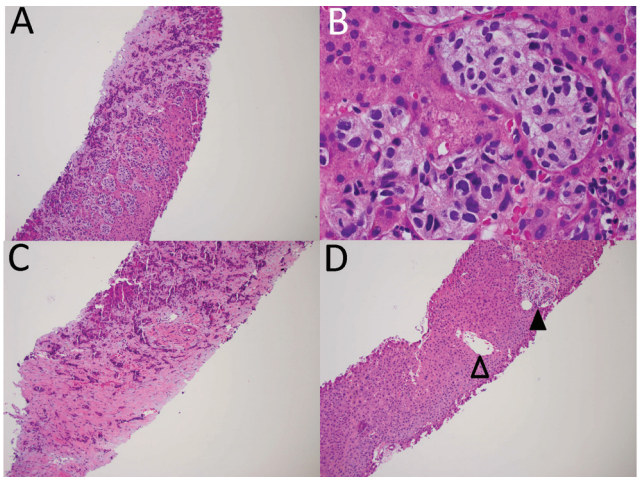

FIGURE 2 Core needle biopsy of liver after cirrhotic changes demonstrated sheets and nests of infiltrative epithelioid and spindle cells, with a prominent fibrotic stromal response under (A) low and (B) high magnification. (C) Tumor infiltrate was accompanied by desmoplasia in some areas. (D) The background hepatic plate architecture was intact, with alternating portal tracts (closed arrowhead) and central veins (open arrowhead) at normally spaced intervals. No evidence of septal fibrosis, hepatocyte atrophy, or inflammation was observed.

daily. However, laboratory studies demonstrated progressively worsening liver status over the ensuing months (Figure 3). The patient died of hepatic failure in July 2010.

2. DISCUSSION

2.1 Differential Diagnosis

Our initial differential diagnosis for the transformation of the patient's liver disease included interval development of cirrhosis, nodular regenerative hyperplasia (NRH), pseudocirrhosis, and other less common forms of advanced liver disease.

Cirrhosis is defined by disruption of the hepatic architecture by bands of septal fibrosis entrapping regenerating hepatocytes, which produce a nodular hepatic contour and capsular retraction on radiography (Table II). Nodular regenerative hyperplasia is an uncommon liver disease in which multiple small regenerative nodules develop in the liver with very minimal associated fibrosis. Alternating zones of atrophic and hypertrophic hepatocytes are a common histologic feature of NRH, thought to be associated with venopathy in the portal microcirculation from thrombosis or obliteration (Table II) [2,3]. Increased intrahepatic resistance from either cirrhosis or NRH can produce portal hypertension and its sequelae, although symptoms from portal hypertension are uncommon in NRH. Our patient's liver appeared cirrhotic on CT imaging [Figure 1(F)], and although she developed signs and symptoms of portal hypertension, she had neither risk factors for cirrhosis nor laboratory results suggestive of chronic liver disease. In a patient with metastatic disease and without common risk factors for cirrhosis, biopsy and histology are necessary to confirm the diagnosis regardless of clinical and radiographic data. In this case, liver biopsy revealed diffuse carcinomatous infiltration (Figure 2) rather than features of cirrhosis or NRH, suggesting pseudocirrhosis.

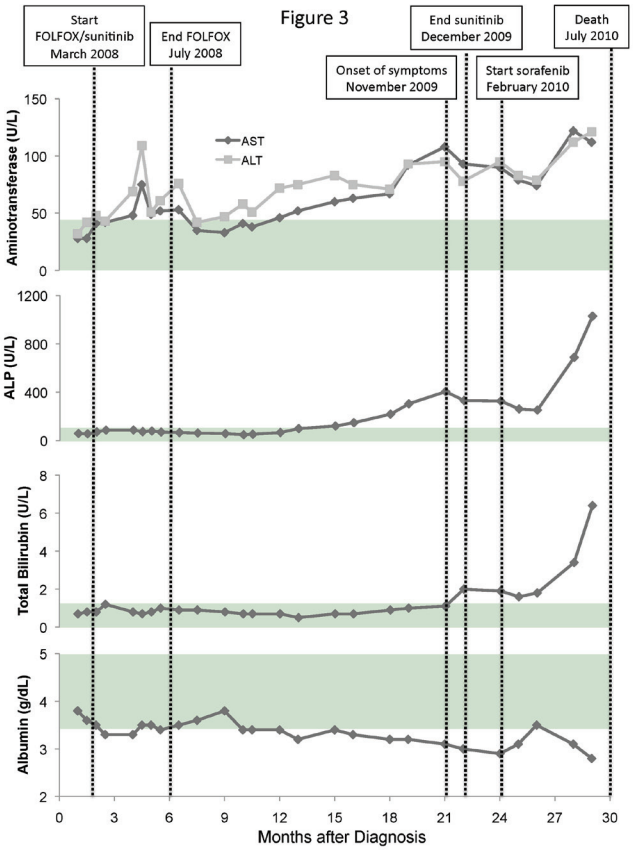

FIGURE 3 Laboratory tests reflecting liver status are charted from the time of diagnosis in January 2008 to the time of death in July 2010. Important landmarks in the patient's disease and treatment are marked. Shaded regions represent the normal range of laboratory values. AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase.

In contrast to cirrhosis, pseudocirrhosis has been defined as a lobular hepatic contour, lobar or segmental volume loss, and caudate lobe enlargement in the absence of septal fibrosis (Table II) [4]. The most frequently reported cause of pseudocirrhosis is metastatic breast cancer treated with chemotherapy [4–14], which commonly presents with diffuse nodular changes of the liver surface on CT imaging [15]. However, the liver can also become nodular and resemble cirrhosis after hepatic metastasis in pancreatic, esophageal, and small-cell lung cancer [16–18]. To our knowledge, pseudocirrhosis has not been reported in metastatic MTC.

Pseudocirrhosis in the setting of cancer may be a hepatic response to chemotherapeutic agents or infiltrating tumor [8]. The latter is called carcinomatous cirrhosis, even though the histologic features of cirrhosis—septal fibrosis with regenerative nodules—are not present. A determination of the cause of pseudocirrhosis is often confounded both by the presence of liver metastases and by the patient's exposure to multiple chemotherapy regimens.

Although histology is required to distinguish between cirrhosis, NRH, pseudocirrhosis, and other forms of advanced liver disease, serial imaging is important to monitor the size of hepatic metastases and therapeutic effect. Our patient was followed with interval PET/CT imaging without intravenous contrast, which permitted visualization and measurement of the liver metastases after FOLFOX–sunitinib therapy [Figure 1(D)], but which may have missed subtle morphology changes in the liver throughout the course of her disease.

2.2 Toxicities of FOLFOX and Sunitinib

Because many chemotherapeutic agents (such as tamoxifen, cyclophosphamide, and methotrexate) have been implicated in pseudocirrhosis [4,5,12], we considered the possibility that treatment effects

TABLE II Causes, characteristic findings, and treatment of cirrhosis, nodular regenerative hyperplasia, and pseudocirrhosis

Variable	*Cirrhosis*	*Nodular regenerative hyperplasia*	*Pseudocirrhosis*
Causes	Alcohol Viral hepatitis Biliary disease Primary hemochromatosis Wilson disease α_1-Antitrypsin deficiency	Pathogenesis unknown; possibly results from venopathy in the portal microcirculation because of thrombosis or obliteration related to hypercoagulability, endothelial cell damage, or autoimmune injury	Chemotherapy or metastatic carcinomas, particularly of the breast
Clinical manifestations	Complications of portal hypertension Hepatic encephalopathy Spider angiomata Palmar erythema Gynecomastia	Often asymptomatic, with normal liver chemistries Preserved hepatic function with complications of portal hypertension in symptomatic patients	Complications of portal hypertension
Histology	Parenchymal nodules of proliferating hepatocytes encased by fibrosis Fibrous septa bridging portal tracts and hepatic veins Disruption of the global hepatic architecture	Parenchymal nodules of hypertrophic hepatocytes centrally and atrophic hepatocytes peripherally Absence of fibrous septa with occasional periportal or perisinusoidal fibrosis Findings best appreciated on reticulin stain	Fibrosis and desmoplasia in areas of infiltrative carcinoma Entrapped residual hepatocyte nodules may appear regenerative Areas of intact hepatic architecture normally present
Radiography	Nodular liver with caudate lobe hypertrophy Evidence of portal hypertension, including varices, splenomegaly, and ascites	Poor sensitivity and specificity Evidence of portal hypertension, including varices, splenomegaly, and ascites	Same as for cirrhosis Possible regression of discrete hepatic metastases on serial imaging
Treatment	Treatment of the underlying causes and complications of portal hypertension Liver transplantation Surveillance for hepatocellular carcinoma	Elimination of causative factor, if established Treatment of complications of portal hypertension	Withdrawal of hepatotoxic agent if chemotherapy-induced, or treatment of underlying disease in carcinomatous disease Treatment of complications of portal hypertension

may have contributed to our patient's liver disease. Although not directly associated with pseudocirrhosis, 5-fluorouracil, oxaliplatin, and sunitinib may cause other adverse events affecting the liver. For example, in 27 patients with colorectal metastases to the liver, 47% developed hepatic steatosis with 6–12 cycles of 5-fluorouracil and leucovorin [19]. In a similar cohort of patients awaiting hepatectomy, neoadjuvant FOLFOX (compared with no pre-surgical treatment) increased the risk of hepatic steatosis and sinusoidal obstruction [20]. Sinusoidal dilatation is a common adverse event with oxaliplatin that can cause noncirrhotic portal hypertension in patients with stage III or IV colorectal cancer [21,22]. In a report of pseudocirrhosis in the setting of metastatic pancreatic cancer, the liver appeared normal after discontinuation of gemcitabine and oxaliplatin, but that change was also accompanied by primary tumor regression and reduction in the CA19-9 tumour marker, suggesting that metastatic disease may have

been responsible for cirrhotic changes in the liver [16]. In general, there is little to no evidence that adverse effects from FOLFOX can mimic cirrhosis.

Sunitinib can cause hepatotoxicity, including acute hepatitis and fatal fulminant hepatic failure, and it should be discontinued after grades 3 and 4 hepatic adverse events [23–25]. However, sunitinib has also been shown to be protective of the liver. In a study of cirrhotic rats, sunitinib decreased hepatic vascular density, inflammation, collagen expression, and portal pressure [26]. In the present case, the liver developed a nodular contour with capsular retraction while the patient was receiving maintenance sunitinib, but 15 months after discontinuation of FOLFOX (Figure 3). Her cumulative exposure to FOLFOX was 4 months and to sunitinib, 20 months. Between the discontinuation of FOLFOX and the onset of symptoms related to portal hypertension, aminotransferases gradually increased, but hepatic synthetic function was preserved (Figure 3). Considering the transformation of discrete hepatic metastases into a diffuse hepatic infiltrate with evidence for MTC on biopsy and the unrelated toxicities of FOLFOX and sunitinib, chemotherapy is unlikely to have caused this patient's liver disease.

2.3 Treatment Strategy

This patient enrolled in a phase I clinical trial of FOLFOX and sunitinib and was later treated with sorafenib after progression of her metastatic liver disease. Sorafenib metabolism depends on the CYP3A4 and UGT1A9 hepatic enzymes. Because the patient's Child–Pugh score ranged from 5 to 8 in the weeks before she started sorafenib, sorafenib was first administered at 200 mg daily and then slowly increased to 400 mg twice daily. Sunitinib and sorafenib were both selected for this patient based on their ability to target the *RET* proto-oncogene, which is central to the pathogenesis of MTC. Activating mutations in *RET* cause multiple endocrine neoplasia type 2, in which MTC is the most frequent neoplasm. In addition, somatic *RET* mutations are common in sporadic MTC and correlate with lymph node metastases at diagnosis and decreased survival [27].

In a phase II study of sorafenib for advanced iodine-refractory thyroid cancer, sorafenib stabilized disease or caused tumor regression in 75% of 30 patients, though MTC was not well represented in the cohort [28]. In another phase II study, 94% of 16 patients with sporadic MTC receiving sorafenib experienced a partial response or stable disease, with a median progression-free survival time of 18 months [29]. Tyrosine kinase inhibitors may also be beneficial in MTC through perturbation of the vascular endothelial growth factor receptor or other signalling pathways in addition to *RET* [30,31].

Considering the disease stabilization with sunitinib and the biologic features of MTC, continued *RET* inhibition was the treatment strategy for this patient.

3. CONCLUSIONS

To our knowledge, this is the first report of carcinomatous hepatic infiltration by metastatic MTC causing clinical and radiographic features of cirrhosis. Liver biopsy revealed diffuse carcinomatous transformation with a prominent fibrotic stromal response and desmoplasia, which is consistent with carcinomatous pseudocirrhosis. Although desmoplasia in a primary tumor has been linked to lymph node metastasis and overall prognosis in MTC [32], few data concerning its presence in metastatic lesions are available.

Histologic characterization is critical for determining whether chemotherapy or liver metastasis is the cause of pseudocirrhosis. Whatever the cause, systemic therapy must be changed to a regimen that can target the underlying disease and that can be used safely in the setting of ongoing hepatic dysfunction.

4. CONFLICT OF INTEREST DISCLOSURES

SGE reports receiving consultation fees and research funding from Pfizer. All other authors report no conflicts of interest.

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