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Research article

Right atrial thrombus in cholangiocellular carcinoma: Case report and a review of the literature

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ABSTRACT

Intrahepatic cholangiocarcinomas are rare, aggressive tumours. We discuss an afflicted patient who had relatively larger thrombi disseminated into the right atrium. A 63-year-old female patient with intrahepatic cholangiocarcinoma referred with complaints of swellings on her face, upper half of her body, and both arms. On contrast-enhanced thoracic CT scans and transthoracic echocardiograms of the patient an intraluminal thrombus measuring 36.3 × 25.7 mm extending to the orifice of the right atrium was seen. Thrombolytics were not successful in reducing the dimensions of the thrombus.

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INTRODUCTION

Intrahepatic cholangiocarcinomas are rarely seen, aggressive, rapidly progressive, highly invasive, metastatic tumours that can be confused with primary or metastatic hepatic carcinomas.[1] They can cause disseminated thrombi in portal and lower extremity veins.[2] Development of thrombosis is not uncommon in cancer patients. However, treatment of thrombosis developed secondary to cancerous formations poses challenging problems. In the light of the literature findings, we discuss a patient with intrahepatic cholangiocarcinoma who had relatively larger thrombi disseminated into the right atrium.

CASE

A 63 year-old female patient referred with complaints of swellings on her face, the upper half of her body and both arms, prevailing for two weeks. Three years ago the patient had undergone segmentectomy for the hepatic segment 8 and her histopathologic examination was reported as 'intrahepatic cholangiocarcinoma; adenocarcinoma of sarcomatoid type, 4/5 metastatic periportal lymph nodes.' The patient did not receive any adjuvant therapy. She had no complaints up to her referral.

Physical examination findings suggest Vena Cava Superior Syndrome (VCSS), such as edematous swellings on both arms, back and face, drowsiness and blue-violet skin discoloration were observed. Besides respiratory sounds auscultated from the left lung were diminished. On contrast-enhanced thoracic CT scans obstruction of the left common bronchus due to compression-invasion of enlarged mediastinal lymph nodes, loss of aeration in the left lung, signs of marked compression, deformation and dilatation of the superior vena cava beginning from the level of aortic knob and an intraluminal thrombus extending to the orifice of the right atrium were seen. Diffuse collateral vascular structures were noted in the superior vena cava (Figures 1 and 2). On transthoracic echocardiograms, a mass consistent with a thrombus measuring 36.3 × 25.7 mm and a grade 3 mitral failure developed because of this mass were observed (Figure 3). Laboratory data is presented in Table 1. The patient was considered inoperable because of her poor performance status and tissue plasminogen activator (t-PA, Alteplase) was given initially as an i.v. bolus dose of 15 mg, then infused at a dose of 0.75 mg/kg for 30 minutes, followed by an infusion dose of 0.5 mg/kg for 60 minutes. Subsequently, acetylsalicylic acid and heparin infusion were started. After 36 hours, since no reduction in the dimensions of the thrombus was observed on transthoracic echocardiograms, a streptokinase (Streptase) infusion was initiated at a loading dose of 250.000 IU/30 min i.v., and then maintained at a dose of 100.000 IU/hr for 24 hours. Any adverse effect related to the usage of thrombolytics was not seen. However daily

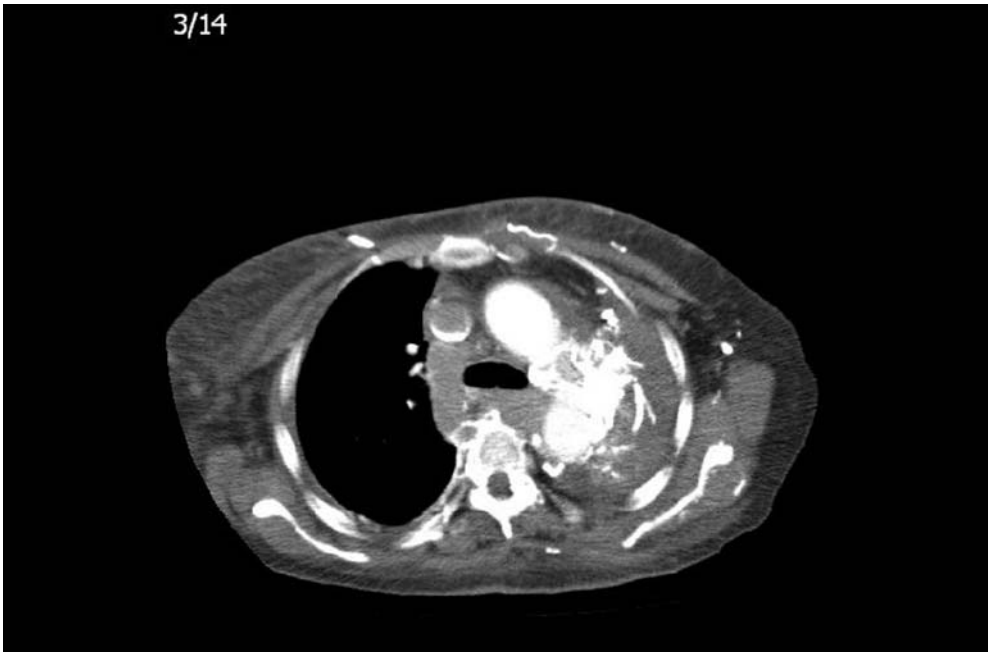

Figure 1. Diffuse collateral vascular structures in the superior vena cava (1).

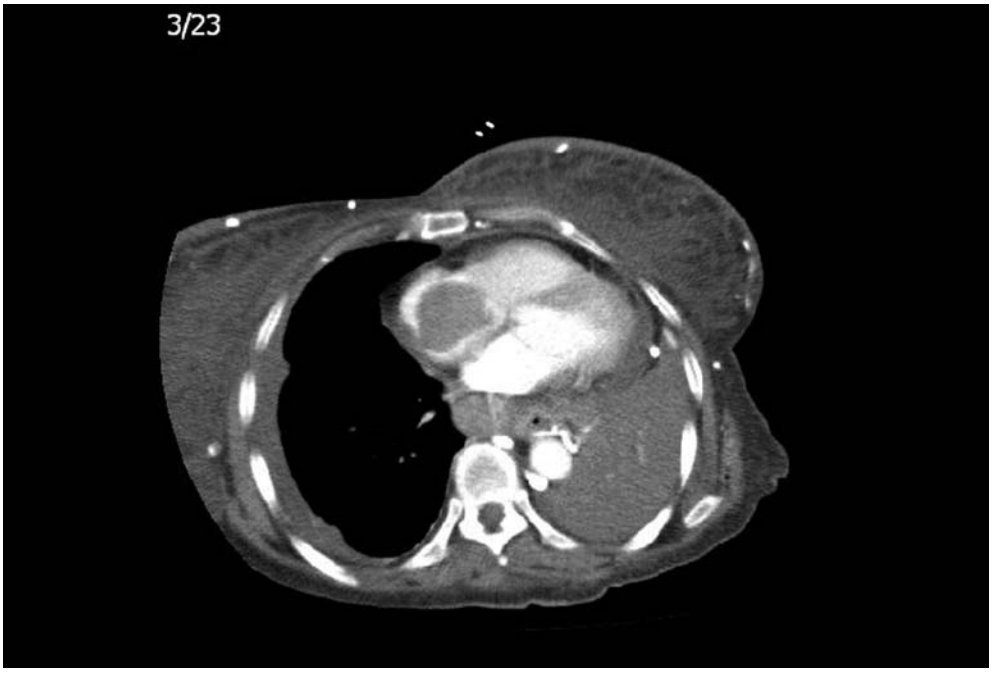

Figure 2. Diffuse collateral vascular structures in the superior vena cava (2).

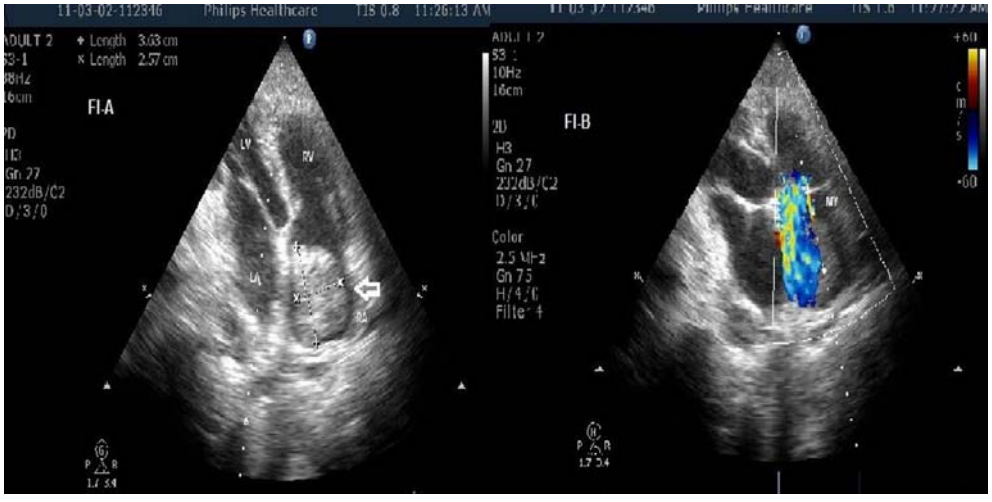

Figure 3. Transthoracic echocardiograms revealed a mass consistent with a thrombus measuring 36.3 × 25.7 mm and a grade 3 mitral failure as a result of this mass.

echocardiographic monitorizations did not demonstrate any marked reduction in the dimensions of the thrombus. Warfarin was started following heparin infusion. Although no reduction in the size of the thrombus within vena cava superior or right atrium was observed, the patient whose dyspnea and edema was attenuated, was discharged after titration of her warfarin dose, so as to keep her INR level within the range of 2.5 and 3. She did not accept the transactions for placement of a vena caval stent and biopsy from mediastinal lymph node(s). The patient is currently in the 5th month of treatment and having 5-Fluorouracil based chemotherapy.

DISCUSSION

Cholangiocarcinomas are relatively invasive and respond poorly to treatment. With the development of ERCP (Endoscopic Retrograde Cholangio-pancreatography) during 1970s, the incidence of intrahepatic cholangiocarcinoma decreased gradually, but its rate of decrease halted within the last two decades.[3]

Table 1. Patient laboratory data.

Laboratory Parameters	Value	Normal Range
Hemoglobin (gr/dl)	11	11.7–16
Platelet count (/μL)	218 × 10^3	150–400 × 10^3
WBC (/μL)	8.52	4.5–11
Alkaline Phosphatase (ALP) (U/L)	280	30–240
Gamma Glutamyl Transferase (GGT) (U/L)	1415	0–30
Alanine Transaminase (ALT) (U/L)	65.8	0–31
Aspartate Transaminase (AST) (U/L)	76.4	0–32
Total/Direct Bilirubin (mg/dL)	0.37/0.21	0.3–1.2/0–0.3
Prothrombin Time (PT) (sn)	12.8	10–14
INR (International Normalized Ratio)	0.9	0.8–1.2
Activated Partial Thromboplastin Time (APTT) (sec)	26.1	22.6–35
Alfafetoprotein (AFP) (IU/mL)	3.33	0–11.3
Ca 19-9 (U/ml)	115.3	0–27
Carcinoembryonic antigen (CEA) (ng/ml)	1.11	0–4.3
D-Dimer (mg/dL) (μg/mL)	0.99	0–5
Fibrinogen (mg/dL)	300	175–400
Anticardiolipin Antibody (ACA) Ig G	Negative	-
Anticardiolipin Antibody (ACA) Ig M	Negative	-
Protein C	Negative	-
Protein S	Negative	-
ANA	Negative	-
Rheumatoid Factor (RF)	Negative	-
Erythrocyte Sedimentation Rate (ESR) (mm/h)	76	0–20
Cryoglobulin	Negative	

Its incidence increases with age. The majority (90%) are adenocarcinomas[4] and are treated like primary hepatic cancers.[5] Adjuvant radiotherapy and a 5-fluorouracil based chemotherapy can be recommended, but with a limited success rate.[6]

Superior vena cava syndrome (SVCS) consists of a collection of symptoms and signs resulting from the obstruction of the superior vena cava (SVC), and is characterized by compromised blood flow in the vena cava because of extrinsic compression or intraluminal occlusion. The condition is usually associated with external compression from intrathoracic masses, most commonly lung cancers and additional known masses of the middle or right anterior mediastinum.[7] Primary or metastatic cancer presenting as an obstructive mass within the SVC is rare.[8] Symptoms of this condition are a constellation of superficial, dilated, vertically oriented and tortuous cutaneous venules or veins above the ribcage margins. In our patient physical examination findings were compatible with SVCS, and also CT scans shows obstruction of the left common bronchus due to compression-invasion of enlarged mediastinal lymph nodes.

In 1865, Trousseau first described the association of occult malignanies and thromboembolic disorders.[9] Abdominal organ adenocarcinomas are more prone to thrombosis. In cancer patients predisposition to thrombosis is related to the degree of activation of hemostatic mechanism. Immobilization, vascular obstruction, surgical interventions, chemotherapy, radiotherapy, bone marrow transplantation and central venous catheters are important causative factors for thrombosis in cancer patients.[10] However in recent years many molecular mechanisms are started to be elucidated.

Imbalance between procoagulant/anticoagulant factors on the endothelial surface increases tendency to thrombosis. As tumour cells interact with monocytes and macrophages the release of tumour necrosis factor (TNF), interleukin-1 and interleukin-2 cytokines is increased. These cytokines lead to shedding of vascular endothelial cells and transformation of a non-thrombotic endothelium into a thrombogenic one.[11] Studies demonstrating the apoptotic role of TNF-α in intrahepatic cholangiocarcinoma are available.[12] Factor VII is activated after its interaction with the subendothelial collagen. Tissue factor (TF), known to be released in relatively larger amounts from adenocarcinomas, also activates Factor VII. It is recognized that a cancer procoagulant is released from gastrointestinal system tumours. Cancer procoagulant activates Factor X and induces coagulation through a common pathway.[13] Mucin released from some cancer cells activates prothrombin *per se* which also initiates the coagulation process via a common pathway. TNF-α and IL-1 can also activate platelet activator factors, PAF and PAI 1, leading to increased thrombocytic activity and a predisposition to thrombosis.[14] TNF-α decreases synthesis of thrombomodulin, attenuates inhibitory actions of factor Va and VIIIa, resulting in increased tendency to thrombosis. Although increased thrombocytic reactivity is held responsible for

enhanced thrombosis in some tumour types, such an increase has not been seen in adenocarcinomas. The increased release of inflammatory cytokines from cancer cells causes expression of thrombomodulin and anticoagulant protein C receptor to decrease.[10]

Studies demonstrating the association between tumoral angiogenesis and thrombosis have been conducted. During neovascularization, it has been advocated that increased release of platelet derived growth factor (PDGF) and platelet derived endothelial growth factor (PDEGF) lead to the formation of para-neoplastic thrombus.[15,16] Vascular endothelial growth factor (VEGF) directly effects endothelium which might enhance activation and adhesion of platelets.[17]

In cancer patients, processes of the coagulation cascade, activation of platelets, accelerated adhesion of endothelial cells, suppressed fibrinolysis and protein C pathway are inhibited, which lead to the development of a hypercoagulable state.

Predisposition to thrombosis is already acknowledged in intrahepatic cholangiocarcinoma. Publications demonstrating potential formation of thrombi in the portal vein, inferior vena cava, iliac and femoral veins, in cases with intrahepatic cholangiocarcinoma, are available.[18,19] Even, in some cases, development of very severe manifestations as phlegmasia cerulae dolens has been reported.[20] One single case of intracardiac thrombus was reported by Tasi in 2004. However those thrombi were localized in the left ventricle.[2] This casen with a large thrombi extending to the right atrium, is the first case report of its kind in the literature. In cancer patients, fibrin-thrombocyte vegetations on heart valves and marantic endocarditis can be seen. Vegetations are usually smaller than 2 mm in size which can not be traced in echocardiograms. Although in a scarce number of patients (4 cases cited) intracardiac thrombi have been observed in cases with renal cell, colon, hepatocellular, lung or adrenal cancer.[21–26]

As demonstrated in various studies, prothrombotic markers increase in number as the size of the tumoral mass and stage of the cancer increase.[27] Formation of a huge thrombi in our patient without any known metastatic lesion and any postsurgical residual mass at baseline, is an interesting phenomenon.

In cancer patients, according to the guidelines from the American Society of Clinical Oncology (ASCO), anticoagulation for prophylaxis against recurrent VTE should generally be suggested, but if anticoagulation is contraindicated inferior vena cava filter could be used.[28] Initial treatment with LMW heparin and for long-term oral anticoagulation vitamin K antagonists are suggested. Re-evaluation of the risk-benefit ratio of ongoing anticoagulant therapy is advised, taking into consideration of the quality of life and life expectancy.

For the relief of vascular thrombotic obstruction thrombolytics are used. All thrombolytics decrease mortality rates secondary to vascular occlusion. Thrombolytic treatment is generally beneficial if applied within a maximum of four hours after the onset of symptoms. In our patient, observance of insufficient thrombolytic activity might be attributed to a delayed application of thrombolytic agents. Although superiority of one thrombolytic over another could not be demonstrated, it is known a 2 hour-infusion of t-PA provides faster fibrinolysis than 12–24 hour infusions of streptokinase or urokinase. Therefore, as a first line therapy, t-PA has been used. Streptokinase binds to plasminogen to form a complex which activates plasmin. However, t-PA, in contrast to streptokinase is more specific to fibrin and fibrin-bound t-PA has gained an increased affinity for plasminogen. In other words, these two thrombolytics have different mechanisms of action. It might be rational to use one of them when the other does not induce any therapeutic response.[29] Unfortunately, this approach was unsuccessful in our patient.

In conclusion, intrahepatic cholangiocarcinoma is a cancer type with heterogenous biologic behaviour and unusual complications. It is very challenging to conduct large scale investigations in these rarely seen diseases. Unusual clinical presentations of these patients should be always kept in mind.

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