Alveolar Echinococcosis of the Liver

Sequelae of Chronic Inferior Vena Cava Obstructions in the Hepatic Segment

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Background: The clinical pattern and long-term course of chronic inferior vena cava (IVC) obstructions are variable and depend on the underlying cause, the segment involved, and the extension of secondary thrombosis. Pertinent data on IVC obstructions in well-defined series of patients are lacking. We report the sequelae of chronic IVC obstructions in the hepatic segment in 11 consecutive patients derived from a cohort of 104 patients with alveolar echinococcosis of the liver.

Methods: Based on the results of computed tomography scans, 11 patients (7 men, 4 women; mean age, 53.4 years) with IVC obstructions were selected from an ongoing prospective long-term chemotherapy trial comprising 104 patients with alveolar echinococcosis studied at yearly intervals according to a protocol. Obstruction of the IVC in the 11 patients existed for a mean duration of 8.6 years. In these patients, magnetic resonance imaging was performed to assess the morphologic features and extension of the IVC obstruction, as well as the collateral venous pathways. Patency and valvular function of the femoropopliteal veins were analyzed by color-coded duplex ultrasonography.

Results: Total occlusions of the IVC were evident in 8 patients (73%) and subtotal stenoses in 3 patients (27%). Only 4 patients (36%) exhibited signs and symptoms of chronic venous insufficiency of the lower extremities; 2 (18%) of the 4 had a history of swelling in the lower extremity. Seven patients (64%) had no lower extremity symptoms. One patient had a history of pulmonary embolism. Abdominal collateral veins were documented in 5 patients (45%) by using magnetic resonance imaging; however, they were clinically evident in only 3 patients (27%). In the 8 patients with IVC occlusion, thrombosis ended at the confluence of the hepatic veins. Obstruction of the IVC was limited to the hepatic segment in 2 patients (18%) and extended to the distal IVC or the iliofemoral veins in 6 patients (54%). Chronic venous insufficiency was present only if the femoropopliteal veins had been involved in the thrombotic process, showing residual venous obstruction, valvular incompetence, or both. Bilateral renal vein thrombosis with moderate proteinuria was observed in 2 patients (18%). The main collateral drainage was achieved through the ascending lumbar, azygos, and hemiazygos veins.

Conclusions: In patients with alveolar echinococcosis, obstruction of the IVC in the hepatic segment often develops asymptptomatically and rarely leads to the impairment of renal function. The collateral circulation fully compensates for obstruction of the IVC. Thrombotic involvement and valvular incompetence of the femoropopliteal veins seems to determine the development of chronic venous insufficiency of the lower extremities.

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Obstructions of the inferior vena cava (IVC) may be caused by a broad spectrum of underlying pathologic conditions. Most often, obstruction of the IVC is the result of acute thrombosis that is frequently associated with malignant neoplasms.1-3 Thrombosis of the IVC originates mainly from the femoropopliteal and iliac veins or may develop primarily in the IVC. Other causes of IVC obstruction include conditions that lead to external compression or constriction of the vein, such as retroperitoneal lymphadenopathy, hepatic masses, aortic aneurysms, retroperitoneal fibrosis, or large adrenal, renal, or pancreatic tumors.2-6 External compression may induce secondary thrombosis of the IVC involving other IVC segments, the renal veins or the iliofemoral veins.

Clinical features of IVC obstruction include leg swelling, the development of chronic venous insufficiency of the lower extremities, the appearance of collateral veins on the abdominal wall, or progressive development of renal failure and nephrotic syndrome.1-3,7-9 The consequences of IVC obstruction depend pri-
For the present study, the medical records of 104 patients with AE included in a prospective chemotherapy trial during the last 20 years were reviewed. The protocol of the study has been published. Briefly, patients were examined at yearly intervals. Control studies included a physical examination, routine laboratory tests, a chest radiograph, and ultrasonography and CT scan of the abdomen.

Thirteen patients with obstructions of the IVC were selected based on repeated CT studies. Two patients had died, leaving 11 patients for the present study (7 men, 4 women; mean age, 53.4 years; range, 33-80 years). For the 11 patients, the mean follow-up after the diagnosis of AE was 12.4 years (range, 3-20 years). The mean time between the diagnosis of AE and the documented obstruction of the IVC was 4.1 years (range, 0-16 years). The mean follow-up period after documentation of the IVC obstruction was 8.6 years (range, 2-16 years). For 4 patients, obstruction of the IVC was documented with CT at the time of diagnosis of AE.

Radical resection of the hepatic manifestations of AE was not possible for any patients. Seven patients underwent a palliative operation, and 4 patients had unresectable AE. Obstruction of the IVC did not occur within 1 year of the operation. All patients received continuous long-term chemotherapy with benzimidazole carbamates (primarily mebendazole). All patients provided informed consent to participate in the present study.

For the present study, complete history and physical examination were obtained. Special attention was given to a history of acute swelling of the lower extremities, deep vein thrombosis, or pulmonary embolism, as well as to signs and symptoms of chronic venous insufficiency of the lower extremities (ie, chronic swelling of the lower extremity, lipodermatosclerosis, hyperpigmentation, and acute or healed ulcers). To assess the morphologic features and the extension of the IVC obstruction, as well as the development of collateral venous pathways, patients underwent magnetic resonance imaging (MRI) of the abdominal and the pelvic vessels in addition to contrast-enhanced CT. The MRI was performed with a 2-dimensional time-of-flight technique using a gradient-recalled echo sequence (Signa, 1.5T; General Electric Medical Systems, Milwaukee, Wis). Color-coded duplex ultrasonography of the femoropopliteal veins was performed to evaluate patency and valvular function.

Alveolar echinococcosis (AE) is a zoonotic infection caused by larval forms (metacestodes) of tapeworms, Echinococcus multilocularis, found in the small intestine of carnivores. The Swiss Echinococcosis Study Group initiated a prospective long-term chemotherapy trial in 1976. A total of 104 patients with AE have been enrolled. Since AE affects the liver in virtually all patients and behaves like a malignant process, patients are prone to the development of an IVC obstruction in the hepatic segment. Based on the computed tomography (CT) scans regularly performed to follow up patients with echinococcosis of the liver, we were able to select 11 patients with chronic IVC obstructions in the hepatic segment. This offered us the unique opportunity to study the consequences of hepatic IVC obstruction in a group of patients with a well-defined underlying cause and level of IVC obstruction.

As documented by CT and MRI, total thrombotic occlusion of the IVC was present in 8 (73%) of 11 patients (Figure 1), whereas in 3 patients (27%), the IVC was subtotally obstructed due to AE-induced compression in the retrohepatic segment.

Only 4 (36%) of 11 patients experienced signs and symptoms of chronic venous insufficiency of their lower extremities. Two of the 4 patients reported an acute episode of swelling of the lower extremity (18% of 11 patients). The other 2 patients had a history of chronic ankle swelling associated with progressive development of lipodermatosclerosis and hyperpigmentation without an acute episode of swelling. Extensive varicose veins of the lower extremities were evident and reported healed ulcers at the ankle region. No patient had active ulcers on the lower extremities. It is noteworthy that in 1 woman, the chronic venous insufficiency had been documented 5 years before the diagnosis of AE, and the subsequent IVC occlusion was documented 3 years thereafter. Chronic venous insufficiency developed in the second patient after occlusion of the IVC was documented. No patient experienced venous claudication. One patient with IVC stenosis had experienced a pulmonary embolism after the IVC obstruction was documented and was, therefore, receiving long-term warfarin sodium therapy. In 7 (64%) of 11 patients, the history and physical examination revealed no signs or symptoms that suggested chronic venous insufficiency of the lower extremities. In 3 (27%) of 11 patients, superficial venous abdominal collateral veins were visible (Table, Figure 2).

In all 8 patients with total occlusion of the IVC, thrombosis ended at the confluence of the hepatic veins.
Total intrahepatic compression of the middle and left hepatic veins by the AE tumor was observed in 2 patients; both had a patent right hepatic vein. One patient had normal liver function, and the other had liver cirrhosis due to chronic viral hepatitis C. In neither patient was the hepatic vein obstruction contiguous to IVC thrombosis. Portal vein thrombosis was present in 3 patients (27%) as an additional consequence of the extensive echinococcosis of the liver (Table).

Distal extension of thrombosis in the 8 patients with IVC occlusion was variable (Table). In only 2 patients was the IVC thrombosis restricted to the segment above the renal veins. In 3 patients, the thrombosis extended from the IVC into the iliac veins. In 1 patient, the thrombosis involved the entire IVC without the iliac veins (Figure 4), whereas in another 2 patients, the iliac veins also were occluded. Among the 6 patients with distal obstruction of the IVC, bilateral renal vein thrombosis was observed in 2. Both patients had moderate proteinuria without evidence of a nephrotic syndrome (ie, normal serum protein level). In 1 patient, the serum creatinine level was constantly elevated (228 µmol/L). In the other 4 patients the renal veins were patent and drained via a collateral network into the azygos and hemiazygos system (Figure 4).

Duplex ultrasonography revealed evidence of involvement of the femoropopliteal veins in 3 patients (27%, Table). In 1 patient with extension of the IVC thrombosis into the right iliac veins, occlusion of the ipsilateral femoropopliteal veins also was evident. In the other 2 patients with thrombosis extending to the distal end of the IVC, intraluminal echogenic septal structures with a thickened echogenic venous wall in the common femoral and superficial veins suggested a late stage of engagement of the infrarenal iliac veins.
thrombotic alterations. One of the latter patients had marked reflux in the femoropopliteal veins of both lower extremities, whereas the other had reflux in the right superficial femoral and the left popliteal veins. Interestingly, 3 of the 4 patients with signs and symptoms of chronic venous insufficiency had insufficient valvular function of the femoropopliteal veins of the affected lower extremity. In the patient with chronic venous insufficiency but a competent deep venous system, extensive varicose veins in both lower extremities with multiple incompetent perforating veins at the level of the ankle were present. This was the patient in whom chronic venous insufficiency had been diagnosed 5 years before the IVC occlusion was observed (patient 3, Table).

On MRI, collateral venous drainage was achieved mainly through the ascending lumbar, azygos, and hemiazygos veins (Figure 1). In all 11 patients, including the 3 patients with high-grade stenosis of the IVC, the azygos and hemiazygos veins were markedly dilated owing to their collateral function for venous drainage. Although in 5 patients the MRI documented superficial abdominal wall veins, the veins were clinically visible as abdominal collateral veins in only 3 patients (Table, Figures 2 and 3), all of whom had thrombotic involvement of the iliac or femoropopliteal veins. In 4 of 5 patients with MRI-documented collateral veins, the flow was cephalad. In contrast, in 1 patient with coexisting portal vein thrombosis, flow in the distal direction was demonstrated in the abdominal veins, suggesting that the vessels served as collateral pathways for the portal circulation.

**COMMENT**

We describe the sequelae of chronic IVC obstructions in the hepatic segment in a well-defined series of 11 patients with echinococcosis of the liver during a mean follow-up period of 8.6 years. In contrast to previous reports, patients were not selected based on clinical signs and symptoms that suggested IVC obstruction but were selected on the basis of repeated CT scans in a large series of patients prospectively followed up because of AE.10

One of the most striking findings of our study was the low rate of signs and symptoms of chronic venous insufficiency. The finding is remarkable since edema of
the lower extremities with development of skin changes, ulcers, or both in the lower extremities are reported to be the most common findings in chronic IVC obstruction.\textsuperscript{1-3,9} Seven of 11 patients reported no episodes of acute swelling of the lower extremities, and no signs and symptoms of chronic venous insufficiency developed after a mean of 8.6 years after IVC obstruction. Although in 3 patients the history encompassed less than 4 years, the patients had no symptoms, and the results of clinical and duplex ultrasonography examinations were normal, thus making future development of chronic venous insufficiency unlikely. In the other patients, the time since the documentation of the IVC obstruction was sufficiently long for the development of chronic venous insufficiency unlikely. Studies that have followed up patients with proximal deep venous thrombosis have found that moderate to severe stages of development of chronic venous insufficiency.\textsuperscript{15-17} Bloodflow studies in patients with isolated iliac vein obstruction and was obviously due to extensive primary varicose veins with multiple incompetent perforating veins in the ankle region. In the 7 patients without symptoms in the lower extremities, IVC obstruction was limited to a level above the renal or iliac veins. In these patients, the femoropopliteal venous valves were competent. Thus, unless valve-bearing venous segments were involved in the thrombotic process, the chance of developing long-term complications in the lower extremities was low. This finding correlates with clinical observations in patients with isolated iliac vein thrombosis or congenital agenesis of the hepatic portion of the IVC (azygos continuation) in whom competent femoropopliteal venous valves prevent the development of chronic venous insufficiency.\textsuperscript{15-17}

The development of an IVC obstruction during a longer time probably contributed to the low rate of symptoms in the lower extremities observed in our patients. Obstruction of the IVC in the hepatic segment occurred as the result of external compression of the vessel due to growth of AE lesions or as the result of strictures known to develop with regression of the larval mass during chemotherapy of AE.\textsuperscript{18} Unlike in acute thrombotic occlusion, the pathogenesis of IVC obstruction in our study most probably allowed collateral pathways sufficient time to develop and to drain blood from the lower extremities without causing substantial venous congestion distal to the obstruction. As demonstrated by MRI, the most important collateral pathways seemed to be the ascending lumbar, azygos, and hemiazygos veins. Notably, in all 3 patients with severe stenosis, marked dilation of the azygos and hemiazygos veins was already present, compensating for the function of the subtotally obstructed IVC.

Visible superficial collateral veins in the abdominal wall are reported to be a common physical sign that develops after IVC obstruction and, therefore, are diagnostically important.\textsuperscript{1-3,7,9} However, in our patients, dilated abdominal veins were observed only occasionally. Although MRI detected abdominal wall collateral veins in 5 patients, they were clinically evident in only 3 patients (Figure 2). All of the patients showed distal extension of secondary thrombosis into the iliac or femoral veins. This confirms previous observations in postthrombotic IVC obstruction that superficial abdominal collateral veins will develop only if the thrombotic obstruction includes the external iliac or femoral veins.\textsuperscript{7}

Several reports have suggested that IVC obstruction involving the renal or the more proximal segment will almost always cause proteinuria and may result in nephrotic syndrome and secondary thrombosis of the renal veins with impairment of renal function.\textsuperscript{2,9} Unlike these reports, in our study, IVC obstruction led only to proteinuria in the 2 patients with additional renal vein thrombosis. Remarkably, in none of our patients was there evidence of nephrotic syndrome. Only in 1 patient with bilateral renal vein thrombosis was the serum creatinine level moderately increased. Similar observations were reported by Jackson and Thomas,\textsuperscript{7} who observed proteinuria in only 3 of 12 patients with IVC thrombosis limited to a level above the renal veins. Our observations suggest that renal function in patients with chronic obstruction of the proximal IVC is mostly preserved and that venous outflow from the kidneys is ensured by an efficient collateral circulation.

Other vascular complications observed in our patients included a history of pulmonary embolism in 1 case, portal vein thrombosis in 3 cases, and segmental obstruction of hepatic veins in 2 cases (Table). Whereas pulmonary embolism in the patient with subtotal IVC stenoses must be regarded as a direct consequence of IVC obstruction, the other vascular complications were related to the invasive nature of the AE tumor of the liver. In particular, there was no evidence that hepatic vein obstructions were contiguous to the IVC, suggesting extension of IVC thrombosis into the liver veins.

Our study of patients with AE of the liver shows that progressive IVC obstruction in the hepatic segment often occurs asymptomatically and that “typical” signs and symptoms are often absent. Venous collateral pathways, particularly the azygos and hemiazygos veins, exhibit a high potential to effectively compensate for the IVC obstruction. The key factor for later development of chronic venous insufficiency seemed to be the extension of secondary distal thrombosis to valve-bearing lower extremity veins, ie, the femoropopliteal veins. Therefore, studies of the deep venous system of the lower extremities are clinically significant in patients with IVC obstruction to estimate the risk for development of chronic venous insufficiency. Impair-
ment of renal function was rarely observed in our patients even if the function of the renal veins was compromised. The rather benign course of chronic IVC obstruction in the hepatic segment is striking and must be considered before interventional therapeutic procedures are considered.

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