Renal Vein Occlusion: Diagnosis and Treatment

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Abstract

Renal vein occlusion in adults is usually a result of vein thrombosis, which is frequently associated with the nephrotic syndrome. The anatomy of renal vascularization is of primary importance for understanding its pathophysiological responses and the clinical and diagnostic presentation of patients with this condition. The reaction of the kidney to its vein occlusion is determined by the balance between the acuteness of the disease, extent of the development of collateral circulation, involvement of one or both kidneys and the origin of the underlying disease. Renal vein occlusion is generally a complication of some other condition, but it may also occur as a primary event. The main goals of therapy should be to conserve renal parenchyma in order to maintain renal function and prevent thromboembolic phenomena.

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Renal venous occlusion due to thrombosis was first described more than a century ago by Rayer [1]. Robinson was the first to apply a ligature around the renal vein in animals in an attempt to produce both complete and incomplete venous obstruction [2]. In more recent times, the first detailed study of an adult patient with renal vein occlusion was published in 1939 by Derow et al. [4]. Since then renal vein occlusion has been recorded in the literature with increasing frequency, amounting to several hundred cases [5-17]. The classic presentation of renal vein thrombosis includes microscopic or gross hematuria, flank pain, a painful palpable mass (in infants), and a decline in renal function. However, this presentation typifies acute thrombosis and is rather infrequent. Most often, renal vein thrombosis is insidious in onset and completely asymptomatic. In many instances, reported literature has not distinguished between an acute and chronic process and unilateral or bilateral vein occlusion.

Renal vein thrombosis is probably not as unusual as has been thought. Due to its asymptomatic nature and the fact that spontaneous recovery occurs more frequently than is clinically suspected, diagnosis is often made at autopsy or not at all. In addition, due to its variable clinical and radiographic findings, renal venous occlusion as a separate entity is rarely diagnosed during life [18-21]. With current imaging modalities, the antemortem and/or presurgical diagnosis can be firmly established. We present here an updated review of the etiology, diagnosis and management of renal vein occlusion.

Etiology

Renal vein thrombosis usually develops as a secondary complication, most notably, the nephrotic syndrome. It may, however, occur as part of a primary disease process. Following is a list of causes:

- *Thrombosis of the inferior vena cava with secondary involvement of the renal veins*. This is a rare occurrence, since ordinarily the inferior vena cava at the level of the kidneys is spared from thrombotic processes due to the rapid efflux of blood from the renal veins, comprising 20% of the cardiac output [5-18].
- *Hypovolemia*. Particularly in infants, gastrointestinal fluid loss leading to dehydration may result in hemoconcentration, sludging and eventual thrombosis in the small renal interlobular veins. This can then spread in both directions to involve the larger vessels [8,9,12]. Other conditions leading to slowing of renal blood flow include cardiovascular disease such as tricuspid valve insufficiency and constrictive pericarditis.
- *Primary renal disease*. In adults, renal vein thrombosis almost always occurs in patients who are nephrotic. The nephrotic syndrome by virtue of it being a hypercoagulable state is associated with an increased incidence of arterial and venous thromboemboli. Hypercoagulability is due to both an increase of prothrombotic factors (increased platelet activation, presence of high molecular weight fibrinogen moieties) and decreased antithrombotic factors (reduced antithrombin III). The incidence of renal vein thrombosis in the nephrotic syndrome ranges from 5% to 62% [8-25] and is most common in membranous nephropathy [12,14,16,23].
- *Occlusion of renal veins by extrinsic or intrinsic involvement of the renal vascular pedicle*. This condition is more common in adults and is usually due to neoplasia; it has been reported in more than 50% of cases of renal cell carcinoma [15]. Other documented malignancies include retroperitoneal tumors and lymphomas. Rarely has extrinsic compression due to an enlarged uterus in pregnancy been described.
- *Systemic disease usually associated with a hypercoagulable state*. In addition to the nephrotic syndrome mentioned above, these comprise such conditions as vasculitis, primary antiphospholipid syndrome, sickle cell disease, and the use of oral contraceptives [24-28].
- *Trauma*. Renal vein thrombosis can be caused by either blunt or surgical trauma. An under-appreciated cause is iatrogenic, namely, venous interventions and the prolonged dwell of catheters in large veins such as the presence of an umbrella as an anti-embolic device, femoral vein catheterization as

a vascular access, and umbilical vein catheterization in neonatal intensive care.

Clinical features

The clinical manifestations of renal vein thrombosis are directly related to the etiology of the occlusion and the response to renal venous hypertension. It is important to remember that the rapidity of the venous occlusion and the development of venous collateral circulation determine the clinical presentation and resultant renal function.

Effective development of the collateral veins probably takes several days [5,22,24]. Since the spectrum ranges from acute complete to chronic incomplete occlusion, a uniform clinical picture is not to be expected. Harrison et al. [8] divided cases into two clinical groups: acute and gradual. In the acute setting renal vein thrombosis may be uni- or bilateral. One or both kidneys are palpable (in children only) and are painful with overlying tenderness and muscle spasm. Routine laboratory tests often reveal hematuria, proteinuria, and a reduction in glomerular filtration rate. Acidosis, leukocytosis and an elevated plasma lactate dehydrogenase may be found [17-21,25]. The affected kidney rapidly increases in size due to marked congestion and capsule distension, and the absence of collateral circulation results in hemorrhagic infarction [17-21].

Renal vein thrombosis usually ensues as a secondary complication, most notably, of the nephrotic syndrome

The gradual group is distinguished by a chronic occlusion of the renal vein and is frequently clinically covert. These patients usually do not present with acute pain or severe renal dysfunction. Clinical signs and symptoms may be minimal or absent or are related to underlying disease, such as: renal thromboembolic phenomenon, retroperitoneal mass, or tumor invasion of inferior vena cava [8-18,25-28]. Therefore, the presence of renal vein occlusion is unsuspected in gradual occlusion and collateral vessels have time to effectively develop, providing adequate venous drainage of the kidney and thus preventing renal damage [25-28]. Laboratory studies lack characteristic changes for gradual venous occlusion. The urine may contain an increased number of red blood cells, and in the absence of primary renal disease the urine shows little protein and few if any abnormal elements. No notable changes in blood count or serum enzymes have been observed [8-18,27,28].

Diagnosis

Radiographic modalities constitute the principal means of confirming the diagnosis. These include:

- P*lain film of the abdomen*. X-rays usually reveal an enlarged kidney during the acute stage (depending upon the rapidity with which occlusion has developed), the completeness of the occlusion and the time lapse between onset of obstruction and clinical observation. In severe obstruction, renal infarction and atrophy ensue and kidney size progressively shrinks. This process may take place over a period of several months [27,28].
- I*ntravenous pyelography*. On IVP, signs indicative of renal vein occlusion include decreased or absent opacification [15,27]. These signs will be seen in the acute phase. It should be pointed out that IVP may appear entirely normal [27,28].
- U*ltrasound* (D*uplex*) *of kidney and renal vein*. This should be the initial investigation of choice. An increase in renal size accompanied by a decrease in echogenicity (due to interstitial edema) can be seen during the acute phase of obstruction. Absence of blood flow in the affected renal vessels is nicely demonstrated on real-time ultrasonography [29,32-34].
- R*enal arteriography* (*venous phase*). This procedure is favored over renal venography by some authors [30,31]. Its advantages include assessment of renal parenchyma, blood flow, and the presence of collateral circulation with no risk of dislodging venous thrombi. However, its lack of detail may be insufficient by itself for definitive diagnosis. The typical arteriographic pattern in acute renal vein occlusion shows an enlarged kidney, poor filling of cortical arteries and no renal drainage. In gradual renal vein obstruction an unremarkable arterial study will be obtained, showing the presence of collaterals in the venous phase of arteriography [32].
- R*enal venography* The less specific findings of arteriography have led most radiologists to regard venography with direct selective catheterization of the renal vein as the most reliable diagnostic procedure [33]. Selective renal venography demonstrates a radiolucent area in cases of incomplete occlusion, or an "amputated" image of the renal vein in case of complete occlusion [32,33].
- C*omputerized tomography*. Conventional CT or CT angiography is useful, particularly when vein occlusion is thought to have been caused by renal or retroperitoneal tumor or aortic aneurysm [35].
- M*agnetic resonance imaging angiography*. MRI is reported to be comparable or superior to CT angiography but is not freely available.

Treatment

The main goals of therapy are the preservation of renal parenchyma and prevention of thromboembolic phenomena. Treatment of established renal vein thrombosis can be divided into measures directed towards the specific cause of the occlusion (primary renal disease, tumors, systemic disease) and those aimed at the thrombus itself and/or its complications. These latter include volume resuscitation, dialysis as necessary, but first and foremost anticoagulation. Current management of renal vein thrombosis has shifted from surgical to medical [32-38].

IVP = intravenous pyelography

Medical therapy is dependent on the acuity of thrombosis and the presence or absence of any hypercoagulable state. Regardless of etiology, heparin anticoagulation is the mainstay of treatment for acute renal vein thrombosis. The duration of anticoagulation is determined by whether an irreversible underlying hypercoagulable condition exists. Patients with a potentially reversible condition should be treated with a standard regimen of intravenous heparin, followed by oral warfarin for 3–6 months. Patients with a permanent hypercoagulable state and those with a severe, unremitting nephrotic syndrome (particularly those with membranous nephropathy and with a serum albumin < 20 g/L) are candidates for long-term or life-time anticoagulation.

Thrombolytic therapy consisting of catheter-directed infusion into the affected renal vein offers an attractive alternative for selected patients with acute renal vein thrombosis. It should be only considered in patients with an acute onset of symptoms and renal dysfunction in whom there is no contraindication for systemic thrombolytic agents [38,39]. Chronic renal vein thrombosis often goes unrecognized and is the more common presentation in adults; there is no role for thrombolytic therapy in this setting [39].

Rapidity of occlusion and the development of venous collateral circulation determine the clinical presentation. In the acute setting, anticoagulation is the mainstay of treatment.

Surgical treatment options are nephrectomy, thrombectomy, and surgery for extrarenal causes (retroperitoneal tumors, aortic aneurysms, vena cava primary tumors). Previous indications for nephrectomy included: a) the thrombosed kidney serving as a nidus for infection; b) the thrombotic process in the renal vein extending into the inferior vena cava and then involving the opposite kidney; and c) the ischemic kidney causing secondary high renin hypertension. These indications are almost all obsolete in the light of modern drug therapy. Nephrectomy has therefore been abandoned in favor of thrombectomy. This procedure has not yielded any dramatic therapeutic results. It probably should be considered only in the rare event of bilateral renal vein thrombosis and renal failure that have not responded to anticoagulation. Of note, surgery does not prevent recurrent thrombosis [7,39].

In summary, renal venous occlusion should be considered a dynamic entity, both clinically and radiographically. Correlation of the clinical and radiographic findings allows the diagnosis to be established with a high degree of confidence. The mainstay of treatment in the acute setting is anticoagulation.

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Capsule

A fly model of polyQ disease

More than 40 human diseases are known to be caused by the expansion of simple repeat sequences, the majority being trinucleotide repeats such as CAG or CGG. However, few models for repeat instability recapitulate the striking features seen in human patients, and few or no therapeutics to clamp repeat instability. Jung and collaborators, in the model organism Drosophila, observed striking CAG repeat instability that recapitulates several key features of human disease, including large repeat expansions, with repeat size variations similar to that of human patients. The pathologic CAG/polyglutamine (polyQ) protein, encoded by the expanded CAG repeat, enhanced repeat instability through an inhibitory effect on a regulatory protein involved in DNA repair and replication.

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Capsule

VEGF as antidepressant

Although the molecular mechanisms of antidepressant action remain unclear, one hypothesis suggests that stimulation of growth factor signaling and of adult neurogenesis in the hippocampus may be implicated in their effects. Warner-Schmidt and Duman investigated the effects of different classes of antidepressants on hippocampal expression of the neurotrophic and pro-angiogenic factor vascular endothelial growth factor (VEGF), which their research group had previously shown to be enhanced by electroconvulsive seizure (ECS) treatment. The abundance of VEGF mRNA increased in the hippocampal granule cell layer of rats treated for 14 days with fluoxetine (a serotonin-reuptake inhibitor) or desipramine (a norepinephrine-reuptake inhibitor), as did the abundance of VEGF in hippocampal homogenates. Pharmacological blockade of the VEGF receptor Flk-1 inhibited the increase in cell proliferation in the hippocampal subgranular zone (SGZ) produced by ECS or by chronic exposure to fluoxetine or desipramine, whereas intracerebroventricular delivery of a VEGF isoform stimulated SGZ cell proliferation. Furthermore, pharmacological blockade of Flk-1 inhibited the effects of desipramine on behavioral responses in chronic and sub-chronic rat models of depression, whereas VEGF had an antidepressant-like effect. Noting that antidepressants promoted the proliferation of hippocampal endothelial cells as well as hippocampal neurogenesis, the authors speculated that this could play a role in the treatment of certain forms of depression that are associated with vascular abnormalities

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