“Atherosclerotic Renal Disease in Elderly”

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Introduction- Atherosclerosis is a generalized and inflammatory vascular disease frequently associated with renal disease and dysfunction (1) and one of the major causes of premature death in the United States today(2,3). Diverse renal vascular diseases, including atherosclerotic renal disease (ARVD), account for more than one third of all cases of ESRD.(4) Atherosclerotic plaques are present in up to 30% of patients with CKD and ARVD is among the common causes of CKD in Western societies(5,6). Atherosclerotic changes in the renal artery are evident in 50% of patients with atherosclerotic disease previously (7) and in 6.8% of adults > 65 years or age, they induce significant (>60%) renal artery stenosis.(8) In this review we discuss the pathogenesis and types of atherosclerotic renal disease in elderly including atherosclerotic renovascular disease and atheroembolic renal disease.

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“Atherosclerotic Renal Disease in Elderly”

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I. INTRODUCTION

Atherosclerosis is a generalized and inflammatory vascular disease frequently associated with renal disease and dysfunction (1) and one of the major causes of premature death in the United States today (2,3). Diverse renal vascular diseases, including atherosclerotic renal disease (ARVD), account for more than one third of all cases of ESRD (4). Atherosclerotic plaques are present in up to 30% of patients with CKD and ARVD is among the common causes of CKD in Western societies (5,6). Atherosclerotic changes in the renal artery are evident in 50% of patients with atherosclerotic disease previously (7) and in 6.8% of adults > 65 years of age, they induce significant (>60%) renal artery stenosis (8). In this review we discuss the pathogenesis and types of atherosclerotic renal disease in elderly including atherosclerotic renovascular disease and atheroembolic renal disease.

II. PATHOGENESIS

Atherosclerosis results from a series of cellular and molecular responses to endogenous and exogenous insults, and cellular events involved early in atherogenesis resemble those triggered in other forms of CKD. Perhaps because glomerular cells mimic some of the characteristics of cells in the vessel wall, atherosclerosis and glomerulosclerosis are postulated as comparable processes (9,10,11)

At an earlier stage, hypertension and atherosclerosis may be intimately linked through their effects on endothelial function. A dysfunctional endothelium allows adhesion of lipid-filled macrophages and consequent chemotaxis and aggregation of inflammatory cells. In large vessels, hypertension favors atherosclerosis progression primarily by accelerating the conversion of fatty streaks to raised lesions (12). Eventually, the vascular lesions can progress to vessel wall necrosis (fibrinoid necrosis, necrotizing arteriolitis, and hyperplastic arteriolosclerosis), which may extend to the glomerulus as well (necrotizing glomerulitis) (13). Upregulation of angiotensin-converting enzyme and angiotensin in the walls of atherosclerotic arteries underscores the role of the renin-angiotensin system in the pathogenesis of atherosclerosis in hypertension. Ang II leading to an increase in reactive oxygen species (ROS) production (eg, superoxide anion) and consequently increased oxidative stress (14). ROS can induce vasoconstriction directly and by decreasing NO bioavailability, resulting in endothelial dysfunction.

III. ATHEROSCLEROTIC RENOVASCULAR DISEASE

Chronic ischemic renovascular disease is an increasingly recognized disorder. The prevalence and incidence of atherosclerotic renovascular disease based upon administrative data in the general population greater than 65 years of age were estimated to be 0.5 percent and 3.7 per 1000 patient-years, respectively. It has been estimated that ischemic renovascular disease may be responsible for 5 to 22 percent of patients with advanced renal failure who are over the age of 50 (16-19).

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a) Clinical Clues

There are a number of clinical findings that suggest an increased likelihood of secondary hypertension, some of which specifically suggest the presence of renovascular disease. These clinical clues are important for a second reason in patients with renovascular disease that is diagnosed on an imaging study performed for some other reason. In such patients, the absence of any of these clues makes it much less likely that the renovascular disease is responsible for hypertension, if present, and therefore makes benefit from percutaneous or surgical intervention less likely. This is an important issue since bilateral (or unilateral) atherosclerotic renovascular disease can be an incidental finding on angiography for peripheral artery disease, occurring in patients with little or no hypertension [20,21]. Such patients do not require therapy directed at the renal vasculature, since there is no evidence that revascularization will improve renal or other outcomes in this setting. A few patients with chronic ischemic renovascular disease are normotensive, which may be due in part to a reduced cardiac output. The clinical clues include

- Onset of hypertension at >55 years of age.
- Accelerated, treatment resistant or malignant hypertension.
- Unexplained difference in kidney size >1.5 cm.
- Recurrent unexplained pulmonary edema.
- Worsening renal function after ACE inhibitor treatment.
- Unexplained renal dysfunction.
- Evidence of peripheral artery disease or CAD.

b) Investigation

Variety of imaging studies are available. The screening test should be

- Readily available
- Noninvasive, nonnephrotoxic
- Provide an anatomic diagnosis
- Indicate its functional significance
- Identify patients likely to benefit from intervention

i. Catheter angiography

Catheter angiography using X-ray and iodinated contrast injected by catheters is the gold standard for the diagnosis of renal artery stenosis. [22] It offers the highest spatial and temporal resolution available for anatomically visualizing main and branch renal artery stenoses. However, this method shows large interobserver variation for the location and grade of stenosis (k concordance coefficients 0.26e0.70). [23,24] An important advantage of catheter angiography is that a hemodynamically significant stenosis can be immediately treated in the same session. Improvements in imaging techniques with greatly increased contrast resolution and optimized catheter shapes, have resulted in reduction iodinated contrast exposure. Use of carbon dioxide or gadolinium instead of iodinated contrast to reduce nephrotoxicity has been explored with equivocal results. This invasive intervention is associated with the risk of contrast induced renal dysfunction, atheroembolic episodes, bleeding, dissection and arterial injury and thus is not a suitable screening technique as RAS is responsible for only a small group of patients with uncontrolled hypertension and renal failure.

ii. Ultrasound

Ultrasounds seem to be an ideal screening modality for RAS as it is noninvasive with low cost and free from risks of radiation exposure and contrast related renal dysfunction. It is observer dependant its accuracy varies between 60 and 90% especially transplant kidney. [25,26] The major drawback of this modality is poor visualization of the entire renal artery missing the highest peak systolic velocity at a stenosis using spectral Doppler tracing. Besides this accessory renal arteries are generally not well visualized. Due to abdominal gas and fat limits the visualization of renal vasculature resulting in increased rate of technical failure in comparison to other modalities. RAS can be both proximal and distal based on certain criteria.

iii. Doppler criteria for RAS

Proximal criteria

These are direct signs obtained at the site of the stenosis. Four criteria are used to diagnose significant proximal stenosis or occlusion of the RA. The first and most important sign is the increase in peak systolic velocity (PSV). Velocities >180 cm/s suggest stenosis of >60%, while an end-diastolic velocity >150 cm/s suggests a degree of stenosis >80%. In a meta-analysis, PSV was the best predictor of RAS, with a sensitivity and specificity of 85% and 92%, respectively. [40] The third criterion is the identification of RAS with no detectable Doppler signal, a finding that indicates occlusion. The fourth criterion is the visualization of color artifacts such as aliasing at the site of the stenosis and the presence of turbulence at Doppler evaluation indicating the presence of a significant stenosis upstream. Usually, these two patterns are the first and immediate signs of a stenosis. [27,28]

c) Distal criteria

The difficulties related to the direct evaluation of the stenosis (the mean examination time was 69 min for the complete examination and 14 min for the distal evaluation) have led several investigators to search for and to identify waveform alterations, other than increased velocity, distal to the stenosis in arterial segments more accessible with Doppler US (i.e., hilar or interlobar arteries). The rationale is that the flow at the renal hilum downstream to a hemodynamically significant stenosis should become damped and show a slow rise to the peak systole. This phenomenon has been called the “tardus parvus” effect. Tardus means
slow and late and parvus means small and little. Tardus refers to the fact that systolic acceleration of the waveform is slow with consequent increase in time to reach the systolic peak. Parvus refers to the fact that the systolic peak is of low height, indicating a slow velocity. A retarded acceleration of less than 3.0 m/s², and increased acceleration time greater than 0.08-0.10 s. However, these findings may be less specific than peak systolic velocity in the main renal artery and ideally should be used to support the diagnosis based on peak systolic velocity.

d) Resistive index

RI measures the degree of intrarenal arterial impedance and is calculated using the following formula: ((PSV - end-diastolic velocity) / PSV). RI values measured in healthy subjects show a significant dependence on age and the area sampled. The values in the main RA are higher in the hilar region (0.65, 0.17) than in the more distal small arteries, and they are lowest in the interlobar arteries (0.54, 0.20). Intrinsic renal diseases (i.e., nephroangiosclerosis, hypertension, tubularinterstitial disease, diabetes mellitus, and severe bradycardia) can cause an increase of RI, even in the presence of normal serum creatinine levels. RI > 0.8 suggests reduced benefit from intervention.(29)

i. Computed tomographic angiography

Advances in CT technology can provide accurate anatomic images of even small renal arteries. A review of 8 studies reveals an average sensitivity of CTA for a diagnosis of significant stenosis of 92% (range 64%-100%), an average specificity of 90% (range 56%-99%), and an average positive predictive value of 88% (range 68%-98%).(25) Compared to conventional angiography, CTA is less invasive with faster acquisition, offers better soft tissue visualization, and allows multiplanar imaging of the renal arteries in any obliquity. The accuracy is comparable to MRA; however, CTA has the risks of ionizing radiation and nephrotoxicity from iodinated contrast agents. Also, when there is severe calcification in the renal arteries, the luminal narrowing may be obscured. However, a major limitation of CTA is that it provides only an anatomic but not a physiologic assessment of the stenosis. So the widely accepted anatomic criterion of a 75% decrease in cross-sectional area for diagnosing severe and significant stenosis to predict the functional significance of the stenosis without considering the influence of renal blood flow may not be correct. A morphologically severe stenosis might not induce a pressure gradient if the artery has slowflow dueto renal parenchymal impairment. There is no benefit from dilating a severe stenosis when the ischemic nephropathy is already end-stage. It is a class I, LOE B recommendation based on ACC/AHA guidelines to establish the diagnosis of RAS in patients with normal renal function.(36)

ii. Magnetic resonance angiography

3-dimensional (3D) gadolinium magnetic resonance angiography (MRA) is accurate for diagnosing renal artery stenosis, comparable to CTA and superior to ultrasound and captopril renography.30-31 The median sensitivity and specificity, compared to conventional catheter angiography, respectively, are 92% and 93.5% without contrast and 96% and 93% with contrast. It not only provides high-quality noninvasive anatomic images but also has the distinct advantage of providing a functional assessment of blood flow and organ function. Some of the divergences in the MRA literature results from some investigators defining stenosis based solely on anatomic criteria. The variety of pulse sequences in MRI that assess organ function complement anatomic information. Combining luminal imaging with functional pulse sequences may offer more comprehensive evaluation of the kidneys without markedly increasing scanning time or cost.

e) Other screening tests

Other noninvasive screening tests, such as an intravenous pyelogram, plasma renin activity, the captopril renogram, and renal vein renin measurements are no longer considered suitable for screening patients because of their poor sensitivity and specificity. Some of the important ones are going to be discussed below.

f) Plasma renin activity

The baseline plasma renin activity (PRA) is elevated in only 50-80 percent of patients with renovascular hypertension. The utility of peripheral PRA is reportedly enhanced when measured in the morning with the patient in the seated position and when indexed against urinary sodium excretion; when measured under these exacting circumstances, a high peripheral PRA is found in 75%e80% of patients with proven renovascular hypertension. A very low PRA (e.g., less than 0.3 ng/mL/h) indexed against a normal urinary sodium excretion in the absence of drugs known to suppress rennin argue against RAS.32 The predictive value can be increased by measuring the rise in the plasma renin activity 1 h after the administration of 25-50 mg of captopril, a rapidly acting ACE inhibitor. The sensitivity and specificity of the captopril renin test have ranged in different studies from 75 to 100 percent and 60 to 95 percent, respectively. The general utility of this test is limited by the need to discontinue antihypertensive medications that can affect the plasma renin activity (such as ACE inhibitors, alpha-blockers and diuretics), the low sensitivity, and somewhat decreased predictive value when compared to the renogram after ACE inhibition.(33)

g) Captopril renogram

Oral captopril (25-50 mg) is given 1 h before the isotope is injected. The efficacy of this test is based
upon the typical ACE inhibitor-induced decline in GFR in the stenotic kidney, often accompanied by an equivalent increase in GFR in the contralateral kidney due to removal of angiotensin II-mediated vasoconstriction. The net effect is that the difference between the two kidneys is enhanced. A marker of glomerular filtration, such as DTPA, or compounds that are secreted by the proximal tubule, such as hippurate and MAG3, have been used. The latter may be more reliable in patients with renal insufficiency. Three criteria were established for diagnosing renal artery stenosis: A percent uptake of DTPA by the affected kidney of less than 40% of the combined bilateral uptake. A delayed time to peak uptake of DTPA, which was more than 5 min longer in the affected kidney than in the contralateral kidney. A delayed excretion of DTPA, with retention at 15 min, as a fraction of peak activity, more than 20% greater than in the contralateral kidney. The sensitivity and specificity of the ACE inhibitor scan may, in high-risk populations, exceed 90 percent for high-grade stenotic lesions and for a successful antihypertensive response to correction of the stenosis. It has got a high negative predictive value (90%).

In 2005 ACC/AHA guidelines suggested that it should not be used as a screening test for the diagnosis of renal artery stenosis. (36)

h) Renal vein renin levels

These measurements are obtained by sampling renal vein and inferior vena cava blood individually. The level of the vena cava is taken as comparable with the arterial levels into each kidney and allows estimation of the contribution of each kidney to total circulating levels of plasma renin activity.

i) Progression

The loss of renal function in renovascular disease can result from a usually reversible consequence of antihypertensive therapy or an irreversible reflection of progressive narrowing of the renal arteries and/or progressive intrinsic renal disease. It is unclear what percentage of renal vascular lesions initially found to be stenosed are physiologically important, leading to hypertension and/or renal insufficiency. Few patients with renal artery stenosis that is incidentally discovered on angiography performed for some other reason (eg, peripheral artery disease) progress to end-stage renal disease at prolonged follow-up. (21)

j) Medical Therapy

The principal specific management options in patients with chronic ischemic renovascular disease are medical therapy, angioplasty (usually with stent placement), and surgery. A systematic review of management strategies for renal artery stenosis in general, including bilateral renal artery stenosis associated with renal insufficiency, concluded that the published evidence was inadequate to draw any robust conclusions [38].

Patients with atherosclerosis should be aggressively treated for secondary prevention of cardiovascular disease. These modalities include aspirin, statins, blood pressure control, cessation of smoking, and, in patients with diabetes, glycemic control. Medical therapy with antihypertensive drugs, particularly ACE inhibitors or angiotensin II receptor blockers (ARBs), can effectively control the blood pressure in most patients with bilateral renal artery stenosis [39]. Although now uncommon, hypertension can be resistant to antihypertensive therapy; such patients may be candidates for revascularization. In addition to issues related to blood pressure control and progressive renal artery atherosclerosis, these patients are also at risk for extrarenal cardiovascular events.

IV. REvascularization

a) Possible indications for intervention

Renal revascularization with surgery or percutaneous techniques may be considered in the following settings [40-43]:

- Severe or refractory hypertension
- Recurrent episodes of flash pulmonary edema
- Possibly, otherwise unexplained progressive renal insufficiency
- An inability to maintain renal function as the systemic blood pressure is lowered, even with medical therapies other than angiotensin inhibition

It has been suggested that stable renal insufficiency in the presence of marked bilateral stenoses is an indication for intervention. However, intervention in the absence of the above indications, such as bilateral significant renovascular disease (or unilateral disease in a single viable kidney) as an incidental finding during coronary angiography, is not recommended [36].

By comparison, variable results relating to renal function outcomes are observed after either surgery or percutaneous interventions. This is an important issue. The observations cited above that progressive renal artery stenosis is common on repeat angiography or Doppler ultrasonography and may be associated with an elevation in serum creatinine does not necessarily mean that intervention for reasons other than the above indications will improve outcomes. Many such patients remain stable with medical therapy alone [44].

When considering revascularization in chronic ischemic renovascular disease, the ability to identify patients likely to benefit in terms of renal outcomes remains difficult. Prolonged renal ischemia can lead to renal atrophy that is characterized histologically by tubular loss and a chronic interstitial nephritis [45-46]. Although nonspecific, an elevated serum creatinine concentration suggests the presence of these irreversible processes.
Older studies suggested that clinically significant functional recovery can be achieved with revascularization if filling of the distal renal arterial tree is seen (thereby allowing bypass to be performed) and if one or more of the following criteria is present [47]:

- Visualization of the collecting system either on an intravenous pyelogram or during the pyelogram phase after renal arteriography.
- Kidney length ≥9 cm.
- The presence of intact glomeruli on frozen section biopsy obtained at the time of surgery.
- Presence of high resistive index.

b) Summary

All patients with atherosclerotic renovascular disease should be treated with risk factor reduction according to current guidelines for secondary prevention of cardiovascular disease.

c) Management

Atherosclerotic renal artery lesions may remain stable or progress over time to greater degrees of stenosis at widely varying rates. There is no consensus about the exact approach and the optimal time to intervene since clinical trial data are limited.

The relative efficacy of surgery and angioplasty with stent placement have not been compared in a randomized trial. However, surgery is associated with an appreciable rate of in-hospital mortality (about 10 percent in a national review in the United States) [48]. As a result, the revascularization procedure of choice in most centers is percutaneous angioplasty with stent implantation [49-52]. This recommendation is based upon clinical experience and the success of stenting in coronary lesions.

When intervention is performed, surgery was particularly recommended in the 2005 ACC/AHA guidelines in patients with multiple small renal arteries, early primary branching of the main renal artery, or require aortic reconstruction near the renal arteries for other indications (eg, aneurysm repair or severe aortoiliac occlusive disease) [36].

V. Renal Atheroemboli

Renal and systemic atheroemboli (also called cholesterol crystal emboli) usually affect older patients with diffuse erosive atherosclerosis. Cholesterol crystal embolization occurs when portions of an atherosclerotic plaque break off and embolize distally, resulting in partial or total occlusion of multiple small arteries (or glomerular arterioles), leading to tissue or organ ischemia [53].

a) Risk Factors

Atheroembolization is a complication of severe atherosclerosis. Thus, risk factors for atheroembolic disease, such as older age, male sex, diabetes, arterial hypertension, hypercholesterolemia, and cigarette smoking, are the same as for the development of atherosclerosis [54-60].

i. Inciting events

Once formed, an atherosclerotic plaque may be disrupted by a variety of inciting events, producing cholesterol crystal emboli. These inciting events can be classified broadly into the following:

- Iatrogenic event, usually induced by angiography, cardiovascular surgery, or anticoagulation.
- Spontaneous event, induced by hemodynamic stress.

Cholesterol crystal embolization is iatrogenic in more than 70 percent of cases [61-62]. It is often seen following manipulation of the aorta or other large arteries during angiography, angioplasty, or cardiovascular surgery. Mechanical aortic trauma, induced by radiological catheters or vessel manipulation/clamping, causing plaque disruption, has a key role [46-48].

Angiography is the most common triggering event, accounting for as many as 80 percent of iatrogenic cases [63-66]. The incidence of clinically apparent atheroemboli after angiography has not been well defined.

It has also been suggested that treatment with warfarin, heparin, or thrombolytic agents may cause atheroemboli, perhaps because anticoagulation may interfere with the healing of ulcerated atheromatous plaques [67-68]. However, anticoagulant-associated atheroembolism is uncommon, even in patients with severe aortic plaque (0.7 to 1 percent) [69-70]. In addition, most patients with atheroemboli associated with anticoagulation have a second potential trigger, usually recent angiography. Anticoagulation is the sole inciting event in only 7 percent of such patients [48].

Hemodynamic stress leading to spontaneous embolization was the most common form in historical reports [71-74]. However, as noted, most cases are now related to iatrogenic triggers.

b) Clinical Presentation

Cholesterol crystal embolization to the kidney typically produces a subacute kidney injury observed several weeks or more after a possible inciting event. Severe hypertension may also be present. Less commonly, acute kidney injury occurring within one to two weeks after the inciting event may be seen, usually in association with massive embolization. Patients with renal atheroemboli are typically older (mean age 71 to 72 years in two large series) have a bland urine sediment [75-76], and have may have peripheral eosinophilia.

However, kidney injury due to atheroemboli is not the most common presentation; rather, it is often found after the patient has presented in some other way.
Atherosclerotic Renal Disease in Elderly

This is likely because, when it occurs, atheroembolism is ubiquitous, affecting varied vascular distributions. Thus, renal disease from atheroembolism is part of a multisystem disorder. The clinical presentation is more frequently related to atheroembolization of the skin (producing “blue toe syndrome”) or livedo reticularis), mesentry (producing intestinal ischemia, gastrointestinal bleeding, or pancreatitis), and/or central nervous system (producing transient ischemic attack, confusion, or visual symptoms). Presenting symptoms may also be subtle and nonspecific, such as fever, myalgias, headache, and weight loss. In addition, patients at risk for atheroembolism are not routinely monitored for worsening kidney function.

Atheroembolism is not uncommon as a cause of acute kidney injury in elderly patients. This was illustrated in a series of 259 patients over the age of 60 years who underwent renal biopsy for acute kidney injury; 7 percent had atheroembolic disease [77].

The renal manifestations of atheroembolic disease are usually different from those seen with clot emboli. Clot emboli primarily occur in patients with atrial arrhythmias or a prior myocardial infarction. They tend to produce complete arterial occlusion and renal infarction, leading to flank pain, hematuria, and an elevated lactate dehydrogenase with relatively normal transaminases [78].

By comparison, atheroemboli are typically nondissecting and irregularly shaped; as a result, they tend to produce incomplete occlusion with secondary ischemic atrophy rather than renal infarction. When time, a foreign body reaction often ensues, causing intimal proliferation, giant cell formation, and further narrowing of the vascular lumen. This reaction presumably contributes to the progressive decline in renal function that often occurs for three to eight weeks after the procedure.

c) Urinary findings

The urine in patients with renal atheroemboli is typically benign with few cells or casts, a finding consistent with ischemic atrophy [79-80]. Proteinuria is usually not a prominent feature, except in patients with underlying diabetic nephropathy; however, nephrotic-range proteinuria (as high as 11 g/day) has been rarely reported [78]. Some patients have an active urinary sediment, including hematuria and, rarely, red cell casts. In this setting, an acute glomerulonephritis or vasculitis may be suspected, particularly if there are extrarenal manifestations.

Eosinophiluria also may be seen if the urine sediment is examined with Hansel's stain soon after the renal atheroemboli [79].

i. Eosinophilia and hypocomplementemia

Two other abnormalities that commonly occur during the acute phase are eosinophilia and hypocomplementemia; these changes may reflect immunologic activation at the surface of the exposed atheroemboli [80-83].

ii. Evaluation and Diagnosis

The diagnosis of renal atheroemboli requires a high index of suspicion and knowledge of the associated risk factors. A clinical diagnosis can be made when a potential inciting event (usually angiography) is followed by the delayed onset of kidney injury (typically several weeks or longer rather than hours or days), particularly when there are signs of extrarenal atheroemboli. Renal biopsy is regarded as the definitive method for diagnosis. Alternatively, biopsy of a skin lesion (if present) is a simple, minimally invasive procedure with a high diagnostic yield. Less commonly, histological confirmation may be made in other organs, such as the gastrointestinal track.

Conversely, renal biopsy is crucial for diagnosis of cases with a chronic, smoldering presentation of renal atheroembolization. A tissue sample is also required to make a definitive diagnosis in patients presenting with a spontaneous (rather than iatrogenic) form of the disorder.

d) Treatment and Prognosis

There is no specific therapy for atheroembolic renal disease. Therapeutic modalities are mostly preventive and supportive. These modalities include statins, aspirin, blood pressure control, cessation of smoking, and, in patients with diabetes, glycemic control. In patients with atheroembolic disease, secondary prevention relies upon removal of the causes of atheroembolism and prevention of new showers of atheroemboli. Consideration should be given in affected patients to withdrawal of anticoagulation and avoidance or postponement of new radiologic and/or vascular surgery procedures, if possible. Observational studies suggest that statin use may be associated with better outcomes [82,83]. A potential benefit of low-dose steroids has been reported in retrospective series [69], but this finding was not confirmed in a prospective study [82].

References Références Referencias


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