Review Article

Role of Pathology in the Decision Making of SFA Chronic Total Occlusion: A Narrative Review Article

Ahmed MT Ghanem[1*], Amira Roshdy Eltabbakh[2]

[1]Nasser Institute for research and Treatment, Cairo, Egypt

[2]Tanta University, Radiology department and medical imaging, Tanta, Egypt

*Corresponding Author: Ahmed Mohamed Taher Ghanem, Department of Vascular Surgery, Nasser Institute for Resarch and Treatment, 1351 Kournish El-Nile, Aghakhan, Cairo 11614, Egypt, Tel: 002-01225060416; Fax: 20-02-02-22039236; E-mail: Profdrghanem2012@yahoo.com

Abstract

Long segment femoral chronic total occlusion (CTO) intervention is considered to be among the most challenging procedures in patients with peripheral artery disease. The anatomical TransAtlantic InterSociety Consensus (TASC) classification in SFA total occlusion may be not enough for the selection between endovascular or surgical intervention. This article reveals the importance of clear understanding and visualization of the detailed pathological nature of the lesion and how it will create a more accurate and safe decision.

Keywords: CTO (chronic total occlusion); SFA (superficial femoral artery); Pathological nature

1. Introduction

Peripheral vascular disease (PVD) is devastating health problem all over the world [1]. Endovascular first strategy revascularization is one of the preferred strategies in many vascular centers. Surgical options should always a ready option for revascularization especially with long CTO 14 lesions. So, Chronic total occlusions (CTOs) of arteries are major challenges for revascularization. The caps of CTO lesions, distal popliteal and proximal tibial lesions and long CTO lesions (more than 50 mm length) are between the most important characteristics. The best decision making (whether endovascular or surgical therapy) in CTO lesions of the superficial femoral arteries (SFA) is the main focus of this article [2].

1.1 Aim of the work

The authors here discuss how the decision of the best method of an intervention in SFA total occlusion is difficult.

The anatomical TASC classification in SFA total occlusion may be not enough for the selection between endovascular or surgical intervention. We try to prove in this article the importance of clear understanding and visualization of the detailed pathological nature of the lesion and how it will create more accurate and safe decision.

2. Multiple Dynamic Forces affecting SFA and its Peculiar Nature

2.1 Shortening and length excess

Femoral and popliteal arteries elongate with age 26 and in peripheral vascular disease (PVD) [3, 4]. Also, during flexion, the artery bends smoothly (instead of acutely) and becomes longer [5]. The SFA shortens about 25% during (90 degrees) knee flexion [6] in comparison to (14%) shortening in the popliteal artery [7]. Also, the unstented portion of the artery tends to flex and bend more than the stented segment of the artery during the flexion, while overlapped stent portion cannot shorten as non overlapped one [7, 8].

2.2 Arterial tortuosity and axial twisting

This factor could be explained by the fact that the natural gliding of the femoral vessels 36 in the fascia of the adductor canal is impaired in the old age due to perivascular fibrosis. The adductor canal plays an important role to prevent traction to the vessel wall [9]. Also, the superficial femoral artery deformations in different fetal position have been proved [10].

2.3 Blood flow, wall shear stress, and early atherosclerotic lesions

Atherosclerotic Lesions and diminished arterial elasticity could result in disturbances of blood flow [5]. Wall shear stress (WSS) is directly correlated with blood flow and viscosity of the blood and inversely with the arterial radius [11, 12]. There is also a strong relation between both increased tortuosity and disturbed hemodynamic patterns in the SFA. Regions of low wall shear stress and disturbed flow were investigated, especially in the adductor canal. Repetitive knee flexions, lead to tortuous SFA with disturbed hemodynamic patterns and could cause atherosclerosis to progress [13]. On the opposite side, frequent movements of the leg lead to changes in the shape of the artery and redistribution of WSS may delay the progression of atherosclerosis [14].

3. Clinical Presentation of CTO in Superficial Femoral Artery

Asymptomatic patients with a reduced ankle brachial index (ABI) but no symptoms may have significant impairment of leg function when tested objectively.

3.1 Claudication

The patient suffered from intermittent claudications experiences leg pain (in the 50 calf, thigh or buttock) while walking and alleviated by rest [15].

3.2 Chronic limb threatening ischemia

Chronic Limb Threatening Ischemia (CLTI) or known also as Critical limb ischemia (CLI) is the most aggressive

form of PAD in approximately 1% of all patients with PAD [16]. It is very important to notice that the natural history of the critical limb ischemia is markedly aggressive in comparison to claudication. CLI is associated with a very high risk of limb loss if not promptly treated [17]. Rest pain and ischemic ulceration or gangrene of the forefoot or toes, representing different manifestations of CLI [18].

4. Options for Treatment

Femoral artery (CFA) or superficial femoral artery (SFA) occlusions (TASC D lesion), bypass surgery is preferable to endovascular treatment [19]. The main etiology for intervention in claudicants is to improve lifestyle, given that the risk of severe clinical deterioration (20%) or major limb amputation (5%) during a 3 to 5 year period is low [20]. Most studies demonstrate that infrainguinal endovascular therapy can be carried out with limited periprocedural risk [21]. Nevertheless, the decision to proceed with infrainguinal endovascular therapy rather than an open surgical approach requires a thorough risk benefit analysis based on the information acquired from the history, physical examination, noninvasive imaging, and diagnostic angiography. Salient features of the history and physical examination, when planning an intervention, include (1) indication (claudication 112 versus critical limb ischemia [CLI]); (2) disease location, extent, and severity; (3) degree of disability and lifestyle limitations; (4) medical comorbidities and anesthetic risk; (5) prior lower extremity reconstructions or interventions; and (6) prospects for long term functional status and survival. Also, detailed discussions of duplex ultrasonography, computed tomographic angiography (CTA), magnetic resonance angiography (MRA), and digital subtraction angiography are crucial [19]. So, We need to weigh both surgical and endovascular modalities to select the best method for intervention.

5. Surgical Bypass… is it the Best Option?

5.1 Bypass versus angioplasty in severe ischaemia of the Leg (BASIL) trial (BASIL–1)

That for patients who lived more than 2 years after randomization, a bypass-first revascularization strategy was associated with a significant increase in survival as well as better amputation free survival. The BASIL trial clearly demonstrated that patients who used prosthetic grafts for the bypass surgery (constituting 25% of the surgical group) experienced decreased amputation-free survival compared with those who received autogenous vein grafts. The BASIL authors concluded that patients who underwent bypass surgery after failed first endovascular therapy experienced significantly worse amputation free survival than did those who underwent bypass first as the initial therapy [22]. Despite Basil study-1 recommends surgical bypass over endovascular management, but we still have major complications related to surgical bypass.

5.2 Lower extremity vein graft failure

Although intimal hyperplasia is the main cause of vein graft failure, but geometric remodeling of the healing vein graft is another important factor [23]. Other factors include diabetes, race and perioperative management could be adjusted with total understanding of the risk of early graft failure. So, bypass surgery is not the best strategy for the

claudicant patients. Also, bypass to the tibial arteries must be reserved to limb salvage situations and every effort should be done to use the autogenous vein [24].

6. Endovascular First Strategy

Because many patients with TASC C/D lesions have medical comorbidities that place them at high risk for surgical bypass and therefore endovascular first strategy still an important alternative. Many centers are now using endovascular first therapy as the main treatment line for TASC-C/D lesions and reserving surgical therapy for failed endovascular therapy. We have acceptable short and mid-term outcomes following endovascular intervention of femoropopliteal artery, but with mixed results on longer term outcomes [25].

6.1 Complications of endovascular treatment

Most of them are minor and can be treated with endovascular therapies. A frequent complication of percutaneous access including bleeding, hematoma and arteriovenous fistula.The angle of approach is believed to be the cause of arteriovenous fistula. A pseudoaneurysm (PSA) also may develop after endovascular techniques if the arteriotomy has not sealed adequately. One of the more common problems in the percutaneous procedures is intimal-medial dissection. Balloon inflation causes stretching and disruptions of of the plaque and overlying intima and occasionally the media that results in a tear or dissection. Embolization is a devastating complication of endovascular procedures. Arterial perforation can result from wire manipulation, implantation and removal of endovascular devices or balloon angioplasty [26, 27]. We need a step forward after TASC classification for decision making in the treatment of total SFA occlusion lesion. We need a clear correlation between pathological features, clinical presentation and anatomical distribution of the arterial lesion.

7. Pathological Nature of Chronic Total Occlusion

In coronaries, a chronic total occlusion is defined as total interruption of the coronary antegrade blood flow of greater than 3 months whether documented angiographically or suspected clinically [28]. The CTO has a body, proximal and distal cap. The proximal cap is often calcified or fibrotic and either tapered or not. The body of the occlusion consists histologically from fibrous tissue, whether loose or dense, calcification, atheroma, lymphocytes aggregates and is mostly has also a neovascularization [29]. Negative remodeling was frequent and particularly with long standing CTOs; while shorter duration CTOs characterized by abundant organized thrombus and large necrotic core. Collateral circulation opacifies the distal cap in most cases and appears to be more tapered than the proximal cap, facilitating wire entry with the retrograde techniques [30, 31].

8. Pathological Stages of Chronic Total Occlusion

Three stages of CTO development have been identified: first two weeks is the early stage, (6-12 weeks) is the intermediate stage and (18-24 weeks) is the advanced one. The early stage was characterized by the formation of the immature extracellular matrix with more proteoglycan and low collagen content as an acute response to the vessel injury. In the early intermediate stage (6 weeks), there is a high negative arterial remodeling, disruption of the

internal elastic lamina, and intraluminal neovascularization. In the later intermediate stage (12 weeks), there is reduction in the blood volume, low proteoglycan content and increase in the collagen with microvessels formation that remains till the advanced stage. There is also reduction in the perfusion with advanced CTO lesion.Bidirectional thrombus formation is considered an essential component of the initiating event in the pathogenesis of human CTO development [32]. The physical properties Four pathological features represent a real obstacle preventing the success of the endovascular technique in the intervention of the long standing CTO lesion (Figure 1). These pathological changes include negative remodeling with the resultant reduction in the vessel size up to 80% by 6 weeks, the tough fibrous proximal cap that studded with collagen, progressive decrease in the proteoglycan content with increase in the rigid collagen content and discontinuity of the microvascular network with reduction in the perfusion of CTO [33, 34].
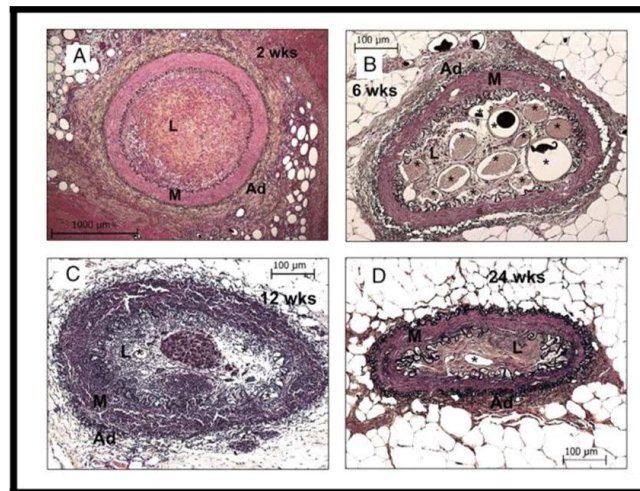

Figure 1: Movat Stained Sections Showing Temporal Changes in Vessel Size and Intraluminal Microvessels. Representative histological sections of occlusions at 2 (A), 6 (B), 12 (C), and 24 weeks (D). There was marked reduction in vessel size at 6 weeks (note the differences in calibration). Microvessels (indicated by *) were maximal at 6 weeks with a decrease at the later time period. Ad-adventitia; L-lumen; M-media [34].

9. Lesion Calcification Classification

Curved multiplanar reconstructions (MPR) as well as axial slices were used for calcification assessment. Depending upon the global amount of calcification on curved MPR, lesions were classified as (1) grade 1, with absent or mild calcification; or (2) grade 2, with severe calcification. On the basis of axial location, lesions were classified as (1) grade 1, with high-density plaque involving less than 50% of the vessel's cross sectional area; or (2) grade 2, with high density plaque involving at least 50% of the vessel's cross sectional area. Only the highest grade was taken in to account in case of multiple types of calcifications [34, 35].

10. Role of Plaque Cap Morphology in Determining CTO Crossing Approach

The CTOP study is the first to categorize peripheral CTOs and identify factors. CTO mapping using the CTOP classification actually increases the rate of crossing without increase the rate of complications.

10.1 Proposed crossing approach based on CTOP classification

CTOP classification represents one of the most detailed and practical algorithm for the selection of the best approach, whether antegrade or retrograde (Table 1) (Figure 2). The retrograde tibiopedal access is mostly used for long (>10 cm) and heavily calcified CTO lesions. We have four types of CTOs depending on the proximal and distal cap appearance. Type I CTO, it could be treated easily with the antegrade endovascular route. Type II CTO, in this type the proximal cap could be crossed with antegrade technique while the distal cap because of the antegrade convexity- needs the retrograde technique or the subintimal route via with antegrade technique. Type III CTO, in this type both antegrade and retrograde techniques have been recommended to be used. Type IV CTO, the retrograde fashion is the best because both the proximal and distal caps have retrograde concavity [36]. (Table 1) (Figure 2).

CTOP Classification	Characteristic
Type I	Two concave proximal and distal caps
Type II	One concave proximal cap, one convex distal cap
Type III	One convex proximal cap, one concave distal cap
Type IV	Two convex proximal and distal caps
Abbreviations: CTOP, chronic total occlusion crossing approach based on plaque cap morphology.	

Table 1: Characteristics of caps in the CTOP study when descend from antegrade approach [36].
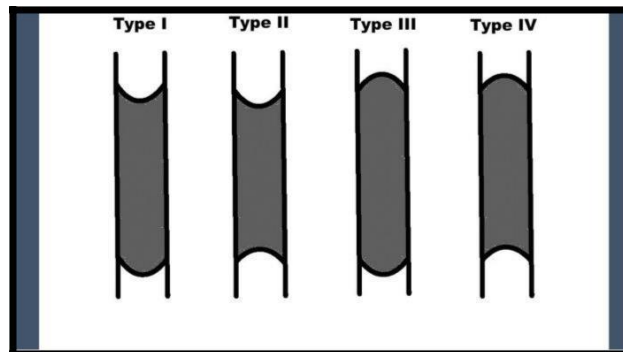

Figure 2: The four types of CTOs based on the proximal and distal cap appearance [36].

11. How the Pathological Nature of Chronic Total Occlusion of SFA appears by Angioscopy

Angioscopy has been used for the imaging of the thrombus, and the vessel wall from inside and the proximal and distal cap of the CTO lesion of the superficial femoral artery. It is generally considered that CTO starts with occlusion of the artery with thrombus, followed by replacement with collagen formation and deposition of calcium. Angioscopy enables direct visualization of the lumen, which makes it useful for the diagnosis of thrombus, but it cannot reach the distal side of CTO lesions in coronary arteries. Therefore, the femoral artery of patients with arteriosclerosis obliterans was examined, and may be, this is the first reported angioscopic finding of the distal side of CTO lesions. In both of our cases, multiple thrombi of variable nature were identified with patchy distribution on the distal side, but not on the proximal side, of the CTO lesions. Those thrombi could   not   be   identified   with

angiography (Figure 3, 4). There was no coagulation disorder in these patients. Our observations support an idea that one mechanism of formation of a long CTO lesion can be the result of a distal extension of the thrombus that started from the initial site of occlusion. The presence of red and mixed thrombi on the distal side of our CTO lesions suggests that the combined use of anticoagulation with antiplatelet agents may be more effective to minimize the extending growth of the CTO lesion [37].
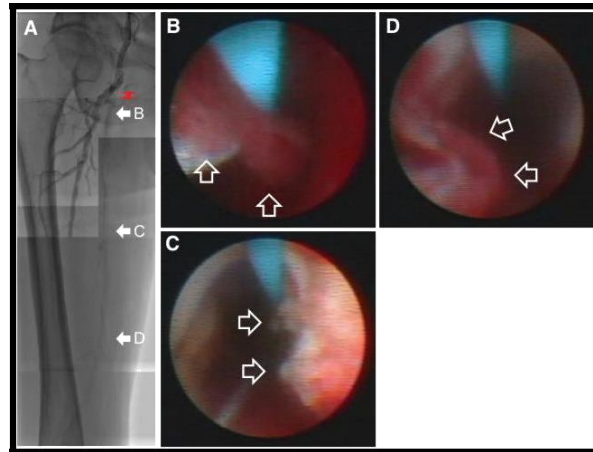

Figure 3: Images of peripheral arterial angiogram and angioscope of preendovascular treatment in case 1. Control angiography (A) showed that the superficial femoral artery (SFA) was occluded immediately after branching of the deep femoral artery (DFA). Collateral circulation from the deep femoral artery irrigated the SFA distal to the occlusion, and its filling with contrast media was observed. The red 2 way arrow indicates the range of chronic total occlusion of the SFA. Angioscopic images (B through D) respectively, correlates with the sites marked by solid arrows in A, and thrombi are indicated by hollow arrows. Different types of thrombi (B, a red thrombus partly covered by white thrombi; C, a white thrombus; D, mixed thrombus) could be identified over the light yellow plaques [37].
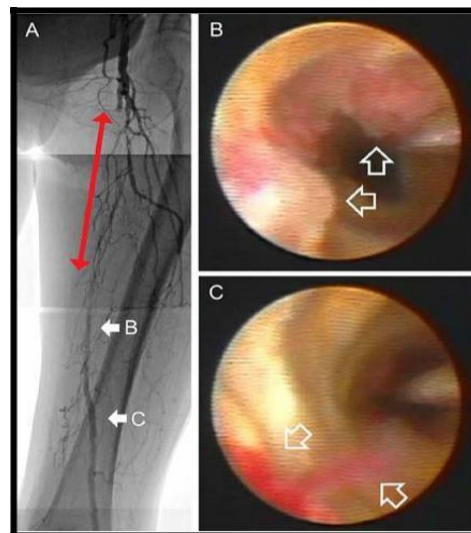

Figure 4: Images of peripheral arterial angiogram and angioscope of preendovascular treatment in case 2. Diagnostic angiography (A) showed that the superficial femoral artery (SFA) was occluded immediately after the

branching of deep femoral artery (DFA), and the distal side of the occlusion was contrast filled by collateral flow from the DFA. The red 2 way arrow indicates the range of chronic total occlusion of the SFA. An Angioscopic image (B and C) respectively, correlates with the sites indicated by solid arrows in A, and thrombi are indicated by hollow arrows. Different types of thrombi (B, white thrombi; C, red thrombus attached with a flapping white thrombus) could be identified over the dark yellow plaques [37].

We need not only to draw the anatomical distribution of the arterial lesion but also the detailed pathological nature of the chronic total occlusion. More calcified hyperechoic lesion will prone to endovascular treatment failure specially at proximal and distal cap. Hypoechoic lesion is a soft lesion that usually will respond successfully to endointervention.

12. Role of Duplex Ultrasound in Describing the Pathology of Chronic Total Occlusion in SFA

Doppler US is a safe and effective imaging modality for functional and morphological assessment of SFA. It can be performed by obtaining gray scale images and the color Doppler study. On a gray scale image, the presence and the size of a plaque could be described, as well as whether the plaque is calcified or not. Three dimensional US has been recently used for measuring plaque volume. On color Doppler ultrasound, total SFA occlusion is seen in the form of absent color signal within the lumen. SFA stenosis shows aliasing artifacts on color doppler Us due to turbulence in blood flow caused by high grade velocities. On spectral flow Doppler, intra-arterial peak systolic velocity (PSV) and ratio of PSV between the site of stenosis and adjacent normal vessel are used as a primary criteria to estimate the degree of stenosis. Stenotic segments will show increase in the peak systolic velocity, which is proportionate to the degree of stenosis. Total absence in spectral flow is seen at totally occluded segments. An area of flow disturbance is seen within 2 cm beyond the area of stenosis due to loss of the laminar flow pattern, it show spectral broadening. Monophasic wave pattern is also described distal to the site of occlusion. It is characterized by a "damped" pattern, which means that systolic flow acceleration is slowed, peak systolic velocity is reduced, and diastolic flow is increased [38]. The use of US is essential in obtaining access, Adequate visualization of vessels, evaluation of proximal and distal CTO cap (morphology, architecture and shape), Length of the CTO, Collaterals at the proximal CTO cap and Calcium content [39].

13. Role of Optical Coherence Tomography in describing the pathology of chronic total occlusion in SFA

Optical Coherence Tomography (OCT) imaging can differentiate between the occluded lumen and the underlying arterial wall in peripheral CTOs. OCT correctly identified tissue composition within the CTO, such as the presence of collagen and calcium and was also able to identify intraluminal micro channels. CTOs could be classified by OCT into different types according to the histological appearance (Figure 5):

1. Extensively calcified wall, dense collagen occupying the lumen.
2. Microcalcifications within the lumen, embedded in collagen.
3. Extensive smooth muscle cell infiltration with collagen in lumen.

4. High lipid content in lumen.

5. Dense collagen within lumen.

In the OCT images, dense fibrotic tissue appeared bright, while highly cellular areas and looser connective tissue appeared darker. Microcalcifications were seen as highly reflective spots under OCT within the CTO that greatly attenuate the OCT signal with depth. Regions of lipids were observed as signal spaces within poor the CTO and confirmed using Oil Red stain. Intraluminal microchannels within the occlusion were identified in most OCT images as small crevices on the longitudinal slices and holes on the cross sectional slices; that were confirmed by histology. The appearance of the different potential components of CTOs under OCT is summarized in Table 2.
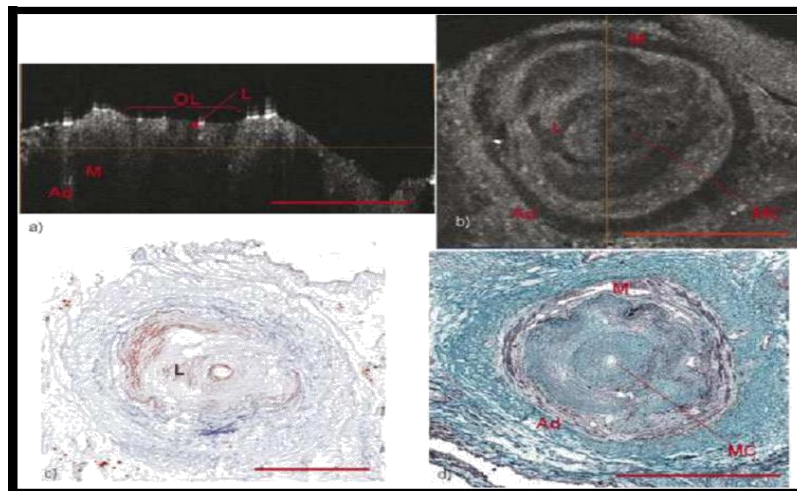

Figure 5: OCT images of an occluded anterior tibial artery demonstrating high lipid content are shown in (a) and (b). A small central microchannel (MC) is seen in both reconstructed cross sectional OCT slices and histology. Lipid deposition, labeled L, is seen both within the collagen matrix of the CTO as well as accumulation around the central microchannel on the Oil Red O histology shown in (c). These regions are seen as weakly scattering regions in the OCT images. Lipid deposition around the central microchannel appears as small segmental deposits seen in the longitudinal OCT image shown in (a). Areas of the lumen containing a high collagen content onceagain appear as bright under the OCT images. Histology is Oil Red O in (c) and Elastin Trichrome (d) [40].

CTO component	OCT appearance
Perivascular tissue (loose connective tissue surrounding the artery)	Dark border surrounding the artery
Adventitia	Signal rich peripheral of the vessel
Media	Signal rich in significant fibrosis or signal poor when it maintains its muscular nature
Collagen within the lumen	Uniformly backscattering region. Denser collagen has a higher back scattering signal.

Smooth muscle cells within the lumen	Dark region within collagen matrix of the CTO. Not very reflective.
Intraluminal microchannels	Fine cracks within the CTO. Residual blood shows as a bright reflective lining.
Lipid	Lightly scattering in large pools.
Microcalcifications within the CTO	Highly reflective dots. When abundant they create shadows.
Intraluminal calcium	Highly reflective in the surface, otherwise signal poor.

Table 2: OCT Signal characteristics of CTO constituents. Quoted from (Nigel R. Munce et al, 2007)

It is clear now that we need a step forward beyond the TASC anatomical classification as a main classification for selection of the best therapeutic approach for the chronic total occlusion of SFA. We need a classification correlates between clinical presentation, anatomical distribution, morphology and pathological nature of the lesion for better therapeutic method selection and better prediction of intervention complications. We have till now a mangel in the available tools to perform this mission, but maybe the duplex scan, optical coherence Tomography and angioscopy are valuable options.

Conflict of Interest
No conflict of interest.

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