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European Association of Urology

Letter to the Editor

Re: Friederike Haidl, David Pfister, Axel Heidenreich. Re: Prostatic Artery Embolization in the Treatment of Localized Prostate Cancer: A Bicentric Prospective Proof-of-Concept Study of 12 Patients. Mordasini L, Hechelhammer L, Diener PA, et al. J Vasc Interv Radiol 2018;29:589–97. Eur Urol 2018;74:525–6

Could Morphologic Changes in Periprostatic Arteries Have an Influence on Prostatic Artery Embolization?

We read with great interest the Words of Wisdoms by Haidl et al. [1] in a recent issue of *European Urology* referring to a paper on prostatic artery embolization (PAE) for localized prostate cancer (PC) by Mordasini et al. [2]. Mordasini et al reported on 12 patients with biopsy-proven low- or intermediate-risk PC who underwent PAE 6 wk before radical prostatectomy (RP). Complete response of the index (dominant) nodule was seen in two patients. However, none of them achieved a complete response and eradication of additional clinically significant intraprostatic nodules. Haidl et al. [1] affirmed that PAE as first-line therapy for localized PC is an unsafe and unsuitable therapeutic procedure, but has potential benefit in a multimodal setting.

Reading the Words of Wisdom and the original paper prompted us to consider that the success of PEA and of intravascular treatments and imaging procedures for prostatic diseases could depend on the morphologic status of the vessels around the prostate, in particular the arteries that supply blood and its contents to the gland. The idea is that if the arteries are diseased, then the flow must be impaired to some extent, thus affecting the prostate gland, and in particular the lesions that are the target of diagnostic and therapeutic procedures. This led us to review slides for our recent RP specimens with a focus on the morphologic status of the arteries (diameter ~1 mm) in periprostatic soft tissues in close proximity to the prostate, located not only posterolaterally but also anteriorly, at the level of the apex, base, and seminal vesicle. While reviewing the slides, a series of questions came to our mind.

Is there a morphologic spectrum of vascular lesions?

We first tried to identify the normal morphologic appearance of the lumen, intima, media, and perivascular tissue of the small arteries (Fig. 1). We then tried to document the types and morphology of vascular lesions. Our aim was not to quantify the frequency or degree of any vascular changes, but rather to identify the spectrum of vascular lesions observed.

We observed the following types of vascular lesion, all associated with variable reduction in lumen size (Table 1):

- Thrombosis of the arteries, that is, endothelial cell detachment and fibrin deposition (Fig. 2);
- Internal elastic lamina fragmentation and reduplication (Fig. 3);
- Medial thickening, thinning, or fibrosis, as well as intimal fibrosis with low vasa vasorum density and lumen narrowing/occlusion (Fig. 4); loss of vessel elasticity

Table 1 – Vascular damage

• Endothelial cell detachment, fibrin deposition
• Intimal thickening, hemosiderin deposition, calcification, inflammation
• Internal elastic lamina fragmentation and reduplication
• Medial thickening, thinning, or fibrosis
• Low vasa vasorum density
• Lumen narrowing/occlusion, loss of vessel elasticity and of endothelial function

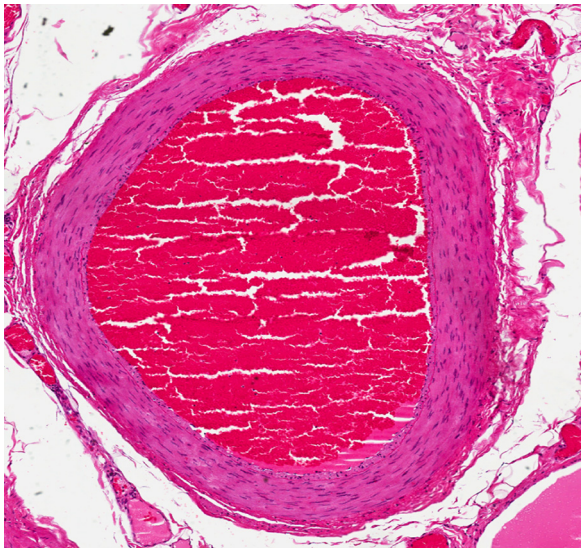

Fig. 1 – Normal artery in periprostatic tissue.

https://doi.org/10.1016/j.eururo.2018.11.026

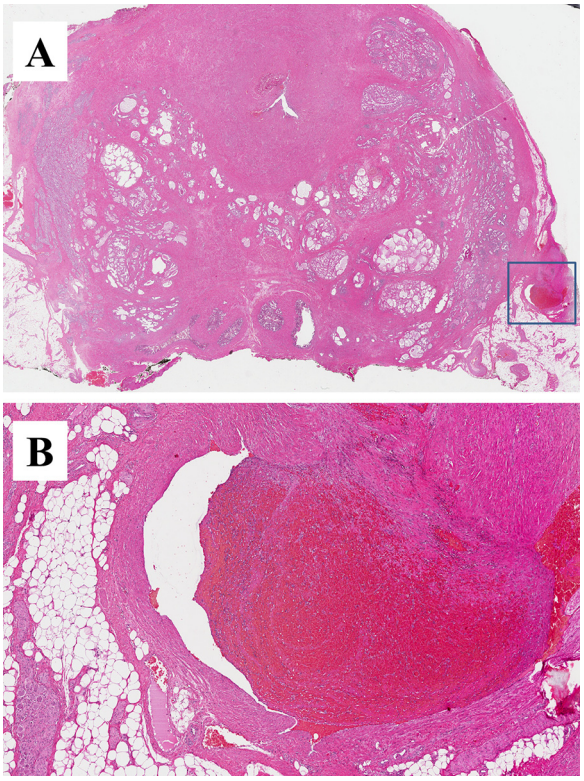

Fig. 2 – (A) Whole-mount radical prostatectomy section with thrombosis of an artery in the periprostatic tissue. (B) Enlargement of the artery contained in the rectangular area, showing endothelial cell detachment and fibrin deposition with lumen occlusion.

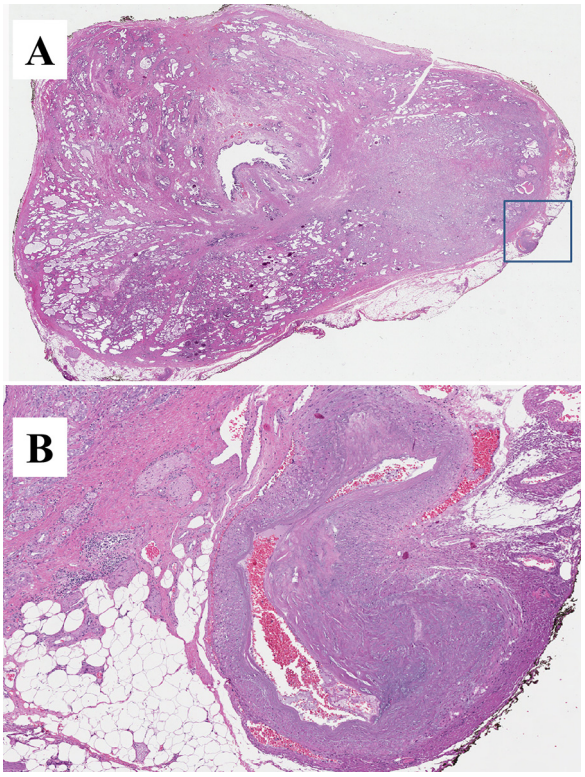

Fig. 4 – (A) Whole-mount radical prostatectomy section with arteriosclerosis involving an artery in the periprostatic tissue. (B) Enlargement of the artery contained in the rectangular area, showing medial thinning, intimal fibrosis, and lumen narrowing.

and endothelial function; and hemosiderin deposition and intimal calcification (Fig. 4);
- Vasculitis (Fig. 5A); and
- Endovascular hemangioma (one case; Fig. 5B).

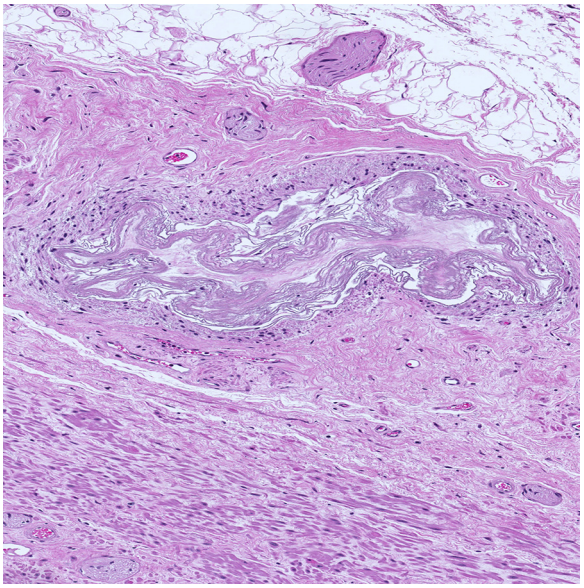

Fig. 3 – Artery with internal elastic lamina fragmentation and reduplication.

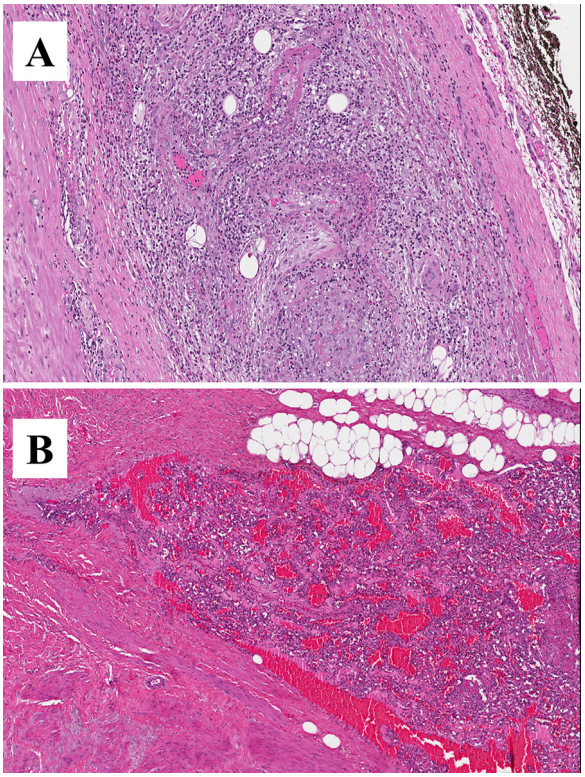

Fig. 5 – (A) Vasculitis with fibrinoid necrosis and inflammatory cells involving an artery in the periprostatic tissue. (B) Endovascular hemangioma.

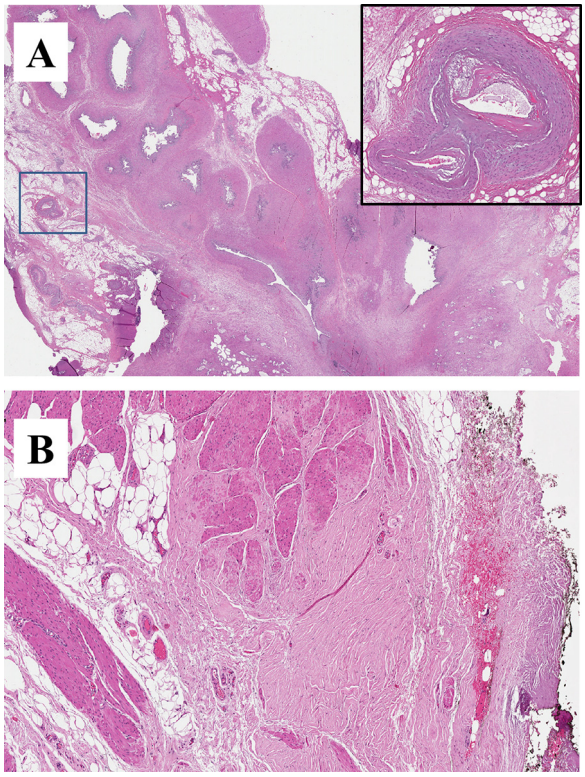

Fig. 6 – (A) Arteriosclerosis in the seminal vesicle enlarged in the upper right corner. (B) Thick fibrosis involving the muscularis propria at the level of the bladder neck (arteriosclerosis present in the adjacent adipose tissue not included in the figure).

There was no predilection in terms of location for the lesions, which were seen not only posterolaterally but also anteriorly at the level of the apex and base, and in the stroma surrounding the seminal vesicle (Fig. 6A).

Is there a relationship between the vascular changes and prostatic diseases?

Studies dealing with vascular changes in and around the prostate are very few. Some of the changes, such as thrombosis of the arteries, could be related to a previous biopsy procedure and/or PC-related coagulation issues.

Haga et al. [3] analyzed the association between atherosclerosis of the prostatic arteries and benign prostatic enlargement (BPE) in surgical specimens. The authors found that atherosclerosis of the prostatic artery was associated with prostate size and concluded that the mechanism underlying this relationship is chronic ischemia, which induces upregulation of the oxidative stress pathways and leads to BPE.

Hager et al. [4] evaluated the association between atherosclerosis of the prostatic arteries and PC. Vascular change was measured as the intima/media ratio (IMR), which is 0.05 in a normal artery. IMR >1 was characterized by a thickened intima compared to the media and a reduced lumen area, that is, an indication of atherosclerosis. IMR >1 was twice as frequent in specimens with PC when compared to tissue without PC; in other words, atherosclerosis of the prostatic arteries was more pronounced in PC-positive than in PC-negative specimens. According to these authors, men with local atherosclerosis are at higher risk of PC.

Lopez-Beltran et al. [5] investigated lymphocytic vasculitis of the transition zone of the prostate gland. The authors found that this type of vasculitis in patients with BPE, associated with infarction of the prostate, "should be considered a form of localized vasculitis with PAN-like morphology that does not necessitate additional evaluation for systemic disease".

In some of our specimens, the bladder neck was present. There was an association in terms of proximity between vascular changes and fibrosis of the bladder detrusor (Fig. 6B) and consequently a reduction in the amount of smooth muscle fibers, partly replaced by adipose tissue. This process is similar to that seen in the myocardium, for which it is thought that epicardial adipose tissue induces fibrosis of the myocardium via secretion adipofibrokines [6]. In some patients this could be responsible for so-called underactive bladder, detrusor underactivity, acontractile bladder, detrusor failure, detrusor areflexia, atonic bladder, chronic retention, and impaired bladder contractility [7]. Chronic bladder ischemia and repeated ischemia/reperfusion during micturition may also induce oxidative stress and denervation of the bladder, thus worsening bladder function [8]. All these events could be related to delayed recovery from lower urinary tract dysfunction or incontinence after radical prostatectomy [9,10].

The diseased arteries in some of our specimens were also seen anteriorly and apically in the prostate. Considering the direction of the blood flow, vascular changes in this location could also be responsible for fibrosis of the cavernous bodies and erectile dysfunction [11].

Is there a relationship between imaging procedures and prostate vessels?

A few studies dealing with imaging procedures and prostate vessels have been published, pointing out directly or indirectly the clinical importance of the vessels. In a study on PAE planning, Maclean et al. [12] found that computed tomography (CT) angiography before PAE can reliably predict arterial morphology and help in planning PAE procedures. Therefore, it should be considered as a preprocedural investigation for men undergoing PAE. Even though not specifically related to the prostate, Humphreys et al. [13] found that comprehensive assessment of pathological, radiological, and clinical correlations in small-vessel disease can shed light on the underlying pathophysiology for magnetic resonance imaging findings for tissues that appear abnormal.

Are the morphological modifications in the arteries reversible?

These vascular morphological modifications could be reversed with physical activity, as it is known that this

prevents cardiovascular disease and erectile dysfunction. In addition, men should be aware of the need to prevent, avoid, or treat diabetes, hypertension, dyslipidemia, smoking, and obesity [14].

Conclusions

A morphologic spectrum of vascular changes is present around the prostate. Such changes could have a role in the development of benign and malignant prostatic diseases. If arteries are diseased, then blood flow is to some extent impaired, thus affecting the prostate gland, in particular the lesions that are the target of diagnostic and therapeutic procedures. Any such morphological modifications might be reversible.

Conflicts of interest: The authors have nothing to disclose.

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November 12, 2018