Journal of Autoimmunity 45 (2013) 80–89

Contents lists available at SciVerse ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Review

Learning from rejection: What transplantation teaches us about (other) vascular pathologies

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ARTICLE INFO

Article history:
Received 28 May 2013
Accepted 30 May 2013

Keywords:
Allograft vasculopathy
Atherosclerosis
Aneurysm
Intimal hyperplasia
Chemokine

ABSTRACT

Allograft vasculopathy is an accelerated intimal hyperplastic lesion leading to progressive vascular stenosis; it represents the major long-term limitation to successful solid organ transplant. Although allograft vasculopathy is not formally an autoimmune disease, nor does it constitute a major cause of cardiovascular disease on a purely numerical basis, its pathogenesis provides an important window on the mechanisms by which immune injury can drive more common vascular pathologic entities. Thus, insights gleaned from vascularized solid organ transplants can shed new mechanistic (and therapeutic) light on: 1) the intimal vascular responses accompanying typical atherosclerosis and other inflammatory vessel diseases (e.g., scleroderma); 2) the pathogenesis of vascular stenosis *versus* aneurysm formation; 3) the sources of intimal smooth muscle cells in the healing of any vascular injury; and 4) the mechanisms by which smooth muscle cells are recruited into intimal lesions. Indeed, research on allograft vasculopathy has led to the understanding that interferon-γ plays a similar pathogenic role in a host of vascular stenosing lesions—and that Th2 cytokines can drive vascular remodeling and aneurysm formation. Moreover, circulating precursors (and not just medial smooth muscle cells) contribute to the intimal hyperplasia seen in atherosclerosis and in-stent restenosis. That non-vessel smooth muscle cells can be recruited to sites of vessel injury further suggests that chemokine and adhesion molecule interactions may be viable targets to limit vascular stenosis in a wide range of vascular lesions. This review will describe the pathogenesis of allograft vasculopathy, and will relate how understanding the underlying pathways informs our understanding of both human transplant-associated disease, as well as other human vascular pathologies.

1. Introduction

Allograft vasculopathy (AV) is a progressive and diffuse intimal hyperplastic lesion of arteries that leads to insidious vessel narrowing, and eventually to allograft ischemia. As opposed to atherosclerosis which typically requires decades before becoming clinically significant, the pace of vessel stenosis in AV is accelerated, accruing over the course of just months to years. Even in an era of immunosuppressive therapies that can effectively block acute cellular and humoral rejection, AV remains the major cause of long-term allograft failure [1]; the "half-life" of most transplanted hearts, for example, remains stubbornly pinned at approximately a decade—largely unchanged since the 1980's [2].

In kidneys, the disease manifests as a progressive renal insufficiency; in liver, ischemic damage is reflected by bile duct drop-out; and in the lung—in addition to the vascular compromise—a kindred process leads to airway narrowing called bronchiolitis obliterans. In cardiac allografts, AV involvement of the coronary and intramyocardial arterioles results in gradual ischemic congestive heart failure and/or lethal arrhythmias.

Although AV has been called "chronic rejection", it should not be considered the consequence of a smoldering parenchymal rejection or even an ongoing rejection of the vessel wall; indeed, AV can progress even in the absence of allospecific responses [3]. Rather, AV is probably better understood as a variation on stereotypical healing. Functionally, the repertoire of vessel responses after injury are extremely limited, and vascular repair—regardless of the underlying cause—ultimately funnels through a final common pathway that conscripts smooth muscle cells and extracellular matrix synthesis to buttress the "damaged" wall. Thus, the vascular wall thickening that accompanies atherosclerosis is a consequence

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0896-8411/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jaut.2013.05.006

of a lifetime of accumulated insults ranging from smoking to hypertension to hypercholesterolemia to diabetes. Similarly, the restenosis that occurs within months to years after venous grafting into arterial circulation or endovascular stenting results from the mechanical trauma (with associated thrombosis and inflammation) of the procedure and/or device. In the case of AV, immune-mediated vascular injury clearly initiates the process, but it is also worth noting that non-immune pathways (e.g., ischemic injury, free radical damage, hypercholesterolemia, etc.) can contribute. This is by way of justifying that lessons to be gleaned from AV will undoubtedly provide pathogenic insights (and suggest potential therapeutic targets) for the more common vascular lesions that confront cardiologists, rheumatologists, and vascular surgeons.

Given that this review appears in *Autoimmunity*, it may also be germane to point out that AV can actually be thought of as a *self-directed* immune response, except that "self" in this case is a transplanted organ. Such AV-associated intimal hyperplasia is also strongly reminiscent of the vascular changes that occur in the setting of scleroderma, where the fundamental target of autoimmune injury *is* the vessel wall [4]. Similar intimal lesions are also seen in vasculitis, where the endothelium and media are subjected to the manifold effects of inflammatory mediators secondarily recruited in the wake of immune complex deposition. Interestingly, graft-*versus*-host disease after mismatched bone marrow transplantation can also manifest as a vasculopathy that entirely mimics AV [5,6].

The following will include an overview of the current thinking regarding the mechanisms that contribute to AV, highlighting the important contributions of innate and adaptive immunity, and emphasizing the role of interferon-γ (IFNγ). Additional insights from animal models and human disease will then be summarized as they pertain to vascular remodeling and aneurysm formation. After encapsulating the experiments that show the various sources of intimal smooth muscle cells, the review will conclude with a discussion of the mechanisms by which intimal smooth muscle cells may be recruited to sites of vascular injury. Throughout, it is worth comparing AV and more common lesions like atherosclerosis (Fig. 1). As noted, they likely share pathogenic mechanisms. Moreover, the relatively accelerated onset of AV makes it more amenable to time-course analysis, and because therapeutic endpoints also occur earlier, AV may well represent a surrogate disease for developing effective interventions.

2. Overview: AV characteristics and pathogenesis [7]

Although allograft veins can develop AV lesions, the most clinically relevant effects are all in the arterial circulation. Thus, even though all vessels should be subject to similar immune injury, an arterial predilection probably reflects the consequences of higher shear stresses. It may also be a consequence of the greater volume of (or functionally different) medial smooth muscle cells. Regardless, it is noteworthy that other vascular pathologies, ranging from atherosclerosis to vasculitis, also preferentially affect arteries over veins.

Atherosclerosis characteristically involves only discrete areas along the artery and is not uniformly distributed; these lesions are also eccentric (the vessel wall is not uniformly concentrically affected), composed of varying proportions of a grummous, necrotic atheromatous core (plus or minuscalcification) and an overlying fibrous cap, composed of smooth muscle cells (SMC) and extracellular matrix (ECM). The underlying media is typically only secondarily affected, largely as a consequence of increased diffusion distance from the lumen, and mechanical atrophy, and the adventitia is usually unchanged. Mononuclear inflammation in atherosclerotic lesions likely drives the disease pathogenesis and is an

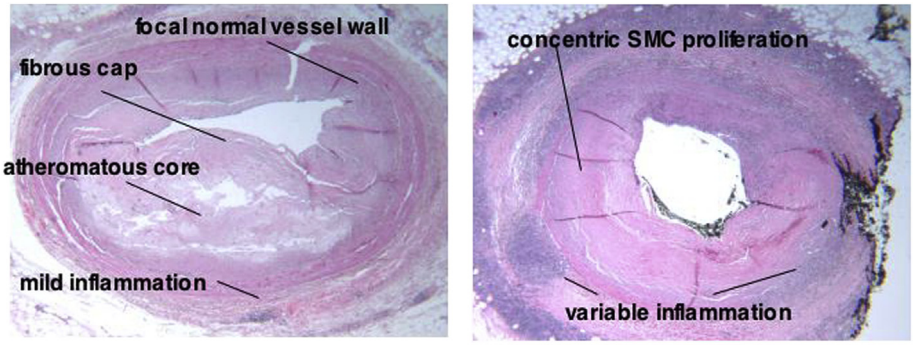

Fig. 1. Atherosclerosis *versus* allograft vasculopathy (AV). Atherosclerosis (left) is driven by a host of vascular insults including hypertension, diabetes, hypercholesterolemia, cigarette smoking, and inflammation. It tends to occur as focal, eccentric lesions with a central atheromatous core including calcification, cholesterol clefts, and necrotic debris, overlying a fibrous connective tissue cap with scattered smooth muscle cells. Atherosclerosis typically requires several years to become clinically significant, although acute plaque rupture with superimposed thrombosis can precipitate abrupt vascular occlusion. AV (right) is initiated by an alloresponse, and is characterized by a concentric intimal hyperplasia composed predominantly of smooth muscle cells and their associated extracellular matrix; it can diffusely involve the entire arterial tree within a transplanted organ, extending from the epicardial vessels into penetrating intramyocardial arterioles. Onset is typically within a few months after transplantation, and becomes clinically significant in 50% of patients within 5 years. Inflammatory infiltrates composed of T lymphocytes, macrophages, and NK cells (visible as blue cellular infiltrates) can be variably present in both, although they tend to be more extensive and diffusely distributed in AV, while more sparse and centered on plaque shoulders in typical atherosclerosis. Intimal hyperplasia accompanying venous grafting into arterial circulations, in-stent restenosis, and the changes associated with chronic vasculitis all show concentric intimal lesions similar to AV, although the initiating mechanisms of injury are presumably different. SMC, smooth muscle cells. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)