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INTRODUCTION

Diseases of blood vessels: Immune system involvement in vasculitis and vasculopathy

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In 1865, a 27-year-old man was hospitalized at the University of Freiburg, Germany, for a rapidly progressive, systemic illness. Over the next month, the patient, a journeyman tailor, would suffer from a strange constellation of symptoms that puzzled his treating physicians. These symptoms included fever, profound weakness, mononeuritis multiplex, and severe abdominal pain. Bedbound and near death, small nodular tumors became palpable in the subcutaneous tissue of the chest and abdomen. The follow year, in the *German Archive for Clinical Medicine*, Adolf Kussmaul, the patient's treating physician, and Rudolf Maier, a collaborating pathologist, reported autopsy findings from the case, in what we would be one of the first descriptions of a form of vasculitis now known as polyarteritis nodosa [1]. Kussmaul and Maier detailed numerous visible nodules that studded the small- to medium-sized arteries of the heart, kidneys, skeletal muscle, and mesenteric vasculature. Accompanying microscopic examination revealed predominantly neutrophilic infiltrate in the media and adventitia of affected aneurysmal arteries. In 1999 in "A History of Early Investigation in Polyarteritis Nodosa" Dr. Eric Matteson, a rheumatologist from the Mayo Clinic, writes "while diseases of the blood vessels have been recognized since antiquity, inflammation of the vessels has only been recognized as a distinct clinical entity for about the past 150 years" [2].

Despite the myriad of scientific and clinical advancements that characterize modern medicine since the time of Kussmaul and Maier, vascular inflammatory diseases continue to challenge clinicians. Prompt recognition of vascular disorders and elucidation of the associated causal factors routinely poses diagnostic dilemmas. The physician evaluating a patient with painful digital ischemia, for example, must quickly decide whether compromised blood flow to the patient's finger is due to inflammation of the arteries (vasculitis) or noninflammatory vasculopathy, including vasospasm, thromboembolic disease, microangiopathy, or another cause. Despite advancements in the understanding of the pathophysiology of most forms of vascular disease, the tools available to physicians to evaluate blood vessel disorders remain suboptimal. Diseases confined to the small (arterioles, capillaries, venules) or medium-sized (visceral) arteries are not readily detected by non-invasive imaging methods, and biopsy of affected tissue or invasive catheter-based angiography remains a critical component of diagnostic evaluation (Fig. 1A). Although biopsy findings often constitute a diagnostic standard for diseases of the small- to medium-sized arteries, accurate sampling of affected tissue, biopsy-related complications, variable confounding effects of concomitant treatment, and subjective pathologic interpretation of tissue findings are common challenges to histologic assessment. In contrast, diseases of the large arteries (aorta and primary branches) are readily visualized by non-invasive angiography but are rarely amenable to biopsy. In absence of histologic evaluation, accurate determination to what extent pathology of the large arteries is driven by inflammation or other factors can be challenging but making this distinction is often critical to the therapeutic decision process. To possibly circumvent this problem, advanced molecular imaging is increasingly used to detect metabolic activity in the walls of larger arteries as a surrogate for vascular inflammation. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) can detect inflammation in the aorta and its primary branches but does not have adequate resolution to visualize small- to medium-sized arteries (Fig. 1B). In the future, novel PET-ligands beyond the non-specific use of FDG may be useful to label

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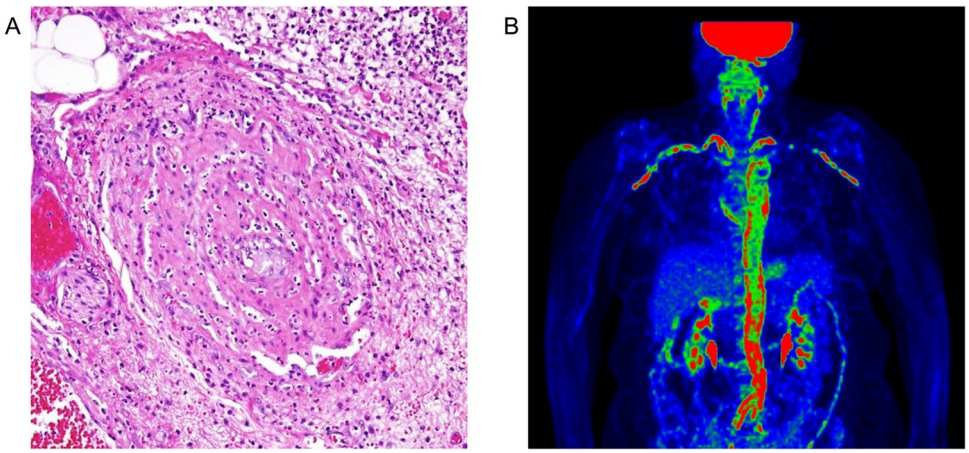

Fig. 1 Use of biopsy material to evaluate small–medium sized arteries and molecular imaging to evaluate larger arteries: Panel **A** is a hematoxylin and eosin stain of resected small intestine from a patient with deficiency of adenosine deaminase 2 (DADA2) demonstrating vasculitic involvement of a medium-sized artery. Panel **B** is an 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan that shows active vasculitis throughout the aorta and branch arteries in a patient with giant cell arteritis (green = moderate FDG uptake, red = severe FDG uptake)

and visualize specific cell populations (e.g., myeloid and lymphoid subsets) and provide much needed imaging-based surrogates to histology in vascular diseases. Improved non-invasive methods to detect the immunologic underpinnings of vascular diseases would greatly aid clinicians trying to make inferences about vascular biology in the absence of direct microscopic evaluation of arterial tissue.

While clinicians often struggle to distinguish immune-mediated forms of vasculitis or other forms of inflammatory vascular involvement from other non-inflammatory forms of vasculopathy, improved understanding of the pathophysiology of many vascular diseases often demonstrates that these kinds of clinical distinctions are rarely absolute. Diseases thought to be solely due to structural defects of blood vessels are often recognized to have complex, immunological underpinnings. The mechanisms of vascular involvement in Marfan's syndrome provide an excellent case study to illustrate the complexity of vascular biology in human disease. Marfan's syndrome is a monogenic systemic disease of connective tissue. Salient features of the condition include ocular lens dislocation, overgrowth of long bones, and aneurysmal involvement of the aortic root with potential catastrophic vascular complications. In 1991, mutations in the *FBN1* gene, which encodes fibrillin 1, were discovered to be causal in an autosomal dominant form of Marfan's syndrome [3]. Structurally in connective tissue, fibrillin 1 monomers aggregate to form microfibrils which cluster around the maturing ends of an elastin fiber. Aortic aneurysms, therefore, were initially assumed to be a consequence of impaired elastin fibers leading to loss of integrity of the vascular wall and subsequent development of a potentially life-threatening, genetically predetermined vasculopathy [4]. Deeper investigation into the pathogenic sequence of vascular disease in Marfan's syndrome, however, revealed an alternative role of fibrillin 1 to regulate the function of transforming growth factor beta (TGFB), a multifunctional cytokine with complex effects on immune cells, cell growth, and apoptosis [5]. Functionally intact fibrillin 1 suppresses the release and activation of TGFB [6]. Inadequate sequestration of TGFB in patients with Marfan's syndrome leads to dysregulated activation of TGFB with downstream phosphorylation of SMAD2/3, subsequent nuclear translocation, and broad transcriptional responses. In Marfan mice, aortic aneurysmal formation can be attenuated by treatment with neutralizing antibodies to TGFB [7]. Additionally, angiotensin 1 can mediate TGFB, and use of losartan, an angiotensin 1 blocking antihypertensive medication, normalized aortic pathology in animal models of Marfan's syndrome [7]. Children with Marfan's syndrome treated with losartan show a tenfold reduction in aortic root growth rate [8]. Noncanonical signaling of TGFB selectively activates extracellular signal-regulated kinase (ERK) 1 and 2 in Marfan mice [9]. Blocking ERK 1 and 2 signaling can suppress abnormal aortic growth in models of Marfan's syndrome. Inhibition of oxytocin, a hormone that stimulates peripheral tissues via ERK1/2 activation, also prevents progression of aortic disease [10]. This example is

highlighted to show that complex signaling events underlie what initially may seem like a straightforward monogenic vasculopathy and to illustrate that therapeutic advances are born from an improved understanding of the pathogenetic mechanisms of vascular disease.

In this issue of Seminars in Immunopathology, the complexity of many forms of vascular diseases are detailed and discussed. *Harper* et al. detail various methods to create patient-specific vascular disease models including use of primary cells derived from various patient biospecimens coupled with in vitro and in vivo vascular models and provide examples of successful approaches to study various rare vascular diseases [11]. *Lee* et al. review the pathogenesis of a monogenic form of vasculitis discovered in 2014 known as deficiency of adenosine deaminase 2 (DADA2) [12]. Similar to Marfan syndrome, a wide array of vascular and non-vascular manifestations can arise from monogenic mutations in a single gene, in this case adenosine deaminase 2 (*ADA2*), which encodes for an enzyme of adenosine metabolism with complex functions that are only just beginning to be understood. *Gloor* et al.review the role of aging as a risk factor for vasculitis [13]. Using Takayasu's arteritis, a disease predominantly of the young, and giant cell arteritis, a disease exclusive to later adulthood, the authors compare age of the host as a critical intrinsic factor that influences the immunologic landscape of different inflammatory forms of vascular disease. *Amancherla* et al. focus on a specific aspect of aging and vascular disease, detailing the connection between acquired genetic mutations in hematopoietic stem cells with subsequent clonal expansion, a process termed clonal hematopoiesis, and risk for atherogenesis and cardiovascular disease [14]. In contrast to the more established associations between germline genetic variation and cardiovascular risk, somatic mutations, acquired later in life and restricted to various tissue compartments, constitute a potentially novel and dynamic way that genetics may shape a range of vascular diseases. *Oliveira* et al. examine potential mechanisms of cardiovascular disease in patients with systemic lupus erythematosus (SLE), a multisystem inflammatory syndrome that affects primarily young women, and illustrate the complex connections between inflammation and accelerated atherogenesis in specific patient populations [15]. *Massicotte-Azarniouch* et al. review the pathobiology of antineutrophil cytoplasmic antibody (ANCA)—associated vasculitis, a group of small–medium vessel vasculitides, with focus on how discovery of pathogenic antibodies can unlock research interest into novel mechanisms of vascular damage [16]. *Knight* et al. review the immune-mediated mechanisms of thrombosis in the context of vascular disease in antiphospholipid antibody syndrome [17]. While thrombotic diseases are often considered non-inflammatory forms of vasculopathy, mechanisms of immune-mediated thrombosis are complex and involve coordinated dysfunction across activated endothelial cells, platelets, and neutrophils. *Galkina* et al. discuss the role of chronic inflammation in atherosclerosis [18]. *Giryes* et al. review the rapidly evolving understanding of vascular involvement in COVID-19 and describe various forms of vasculitis and vasculopathy that can occur in the pulmonary and systemic vasculature in response to a single pathogen [19].

Several themes about vascular diseases emerge from this set of articles. Vascular diseases often involve a complex interplay between cells intrinsic to the vascular wall and invading immune cells. Immune-mediated mechanisms often underlie seemingly non-inflammatory vasculopathies. Insights about vascular biology identified through the study of rare diseases can have implications across a broader spectrum of more common conditions. Mendelian and complex genetics contribute to vascular diseases across the age spectrum. Intrinsic factors such as aging and extrinsic factors such as infectious exposures contribute to vascular pathology. Finally, increasing access to next generation sequencing and other technologic innovations is enabling pathogenetic and therapeutic discovery in vascular diseases at a rapid pace. Translating discovery into the clinic to enable physicians to take better care of patients across a spectrum of rare and common vascular diseases is within reach.

Declarations

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