SHORT COMMUNICATION

The neutrophil to lymphocyte ratio reflects the proteolytic activity of the abdominal aortic aneurysm wall

Carol Green

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ABSTRACT

The Extracellular Matrix (ECM) provides structural support and regulates growth factor bioavailability and cytokine activity, infl uencing cellular function and behaviour that modulate physiologic or pathologic aortic remodelling. Metalloproteinase (MMP) imbalance can stimulate proteolytic activity at the ECM level, resulting in tissue degeneration. Furthermore, MMPs activate a variety of non-matriculated elements, including cytokines and chemokines, infl ammatory processes. Most MMPs have the ability to activate MMP precursors, resulting in an enzymatic cascade capable of amplifying MMP proteolytic activity. Through the overexpression of MMP-9, infl ammatory infi ltrate is the primary source of local proteolytic activity. MMP-2 is physiologically expressed by mesenchymal cells in the middle layer of the aortic wall. These two gelatinases, which are largely expressed in AAA, are thought to be the primary proteolytic enzymes responsible for ECM degradationthe.

Key Words: *Lymphocyte; Abdominal aortic aneurysm*

INTRODUCTION

Aneurysms were initially defined morphologically as a focal loss of parallelism of the vascular wall, which led to progressive dilatation and, eventually, rupture. This definition is now being challenged by the following pathophysiological definition: the progressive loss of the ability to resist high intraluminal pressure due to arterial wall degradation. Because Abdominal Aortic Aneurysms (AAAs) are usually asymptomatic, the current clinical challenge is to diagnose them at an early stage and to decipher the biological mechanisms underlying progressive dilatation and eventual rupture in order to develop new diagnostic and therapeutic approaches.

Extracellular matrix proteins and mesenchymal cells within the aortic media adventitia are required for the structural integrity of the abdominal aorta. Elastins and collagens are the two most common extracellular matrix protein groups. Elastins are an amorphous group of proteins that provide tensile strength to the aorta. In a healthy abdominal aorta, type I collagen outnumbers type III collagen two to three times over, and this ratio is maintained in aneurysmal disease.

Neutrophils are the most abundant type of circulating leukocyte in healthy adults and play an important role in the innate immune response. These diverse cells not only eliminate pathogens, but also act as mediators with specialised functions in health and inflammation. Aside from the numerous strategies used to carry out the tasks of the non-specific, innate immune response, such as phagocytosis, cytokine secretion, and degranulation, neutrophils also contribute to chronic inflammatory conditions through the release of Reactive Oxygen Species (ROS) and neutrophil-derived microvesicles or the formation of Neutrophil Extracellular Traps (NETs). The fact that inflammatory and oxidative stress is implicated in the pathogenesis of cardiovascular diseases has prompted numerous studies focusing on neutrophil-derived biomarkers, which may provide additional clinical benefit and allow [1].

In this review, we discuss the potential biomarker role of neutrophils and neutrophil-derived factors in Abdominal Aortic Aneurysm (AAA) disease and elucidate relevant molecular mechanisms by which these cells are activated in inflammatory conditions. Furthermore, this review may be of interest to both basic scientists and clinicians in order to stimulate translational exchange and innovative clinical approaches.

The goal of this study is to assess the local proteolytic activity at the level of the Abdominal Aortic Aneurysm (AAA) wall and compare the results to the preoperative values of NLRs (Neutrophil-Lymphocyte Ratio), looking for a possible link between the two variables and, implicitly, between the local proteolysis process and the systemic immune response of patients with AAA.

Aneurysm formation is associated with a chronic inflammatory response depletion of the smooth muscle cell population and excessive matrix metalloproteinase (MMP) production resulting in abnormal elastin and collagen degradation1. In vitro models suggest that elastin loss is responsible for early aortic expansion and loss of recoil, whereas collagen breakdown is responsible for late expansion and possibly rupture1. MMP-2 and MMP-9, elastolytic MMPs, appear to play a role in aneurysm formation9. The traditional aortic collagenases MMP-1 and MMP-13 are present in relatively low concentrations in the aortic wall and have substrate specificities that favour the breakdown of collagen types II and III.

Neutrophil collagenase, also known as MMP-8, is a type I collagenase that has been linked to atherosclerosis. Because type I collagen is the most abundant type of collagen in the wall of Abdominal Aortic Aneurysms (AAAs), it was hypothesised that a specific type I collagenase would be involved in the aneurysmal process. The current study sought to identify the extent and location of MMP-8 expression in the normal aorta and AAA wall.

Epidemiology

Aneurysms of the abdominal aorta occur most frequently in men over the age of 65, with a frequency of 1%-5%. The progression of AAAs towards rupture is not linear, but rather presents points of acceleration that can appear at any time. Aortic dilatations, on the other hand, can be stable and asymptomatic for many years, during which time elderly patients may die of other causes. AAAs is more common in women, but they have a higher relative mortality rate than men. When men and women with AAA were compared, it was discovered that women had a significantly higher risk of associated thoracic aneurysms when using gender-specific criteria for normal aortic diameters.

The current study is monocentric, observational, and prospective, and it is taking place at the Department of Cardiovascular Surgery in Cluj-Napoca, Romania. Patients undergoing elective or emergency classical surgery for uAAA or rAAA were included in the study. The study's inclusion criteria were: AAA size greater than 5.5 cm in men and 5 cm in women, symptomatic aneurysms, aneurysm expansion rate greater than 5 mm in 6 months, and/or rupture. We excluded patients with incomplete clinical or paraclinical data, a coexisting diagnosis of acute/subacute bacterial infection, patients requiring preoperative resuscitation manoeuvres, and patients who benefited from endovascular treatment.

Neutrophils account for 50%-70% of circulating leukocytes in healthy adults and are typically the first effector cells at an inflammatory site, recruited

Editorial Office, Journal of Blood Disorders and Treatment, United Kingdom

Correspondence: Carol Green, Editorial Office Journal of Blood Disorders and Treatment, United Kingdom, Email blooddisorder@medicalsci.org

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to form the first line of immune defence against invading microbes. In healthy adults, neutrophil production can reach up to 1011 cells per day, which is regulated by granulocyte colony-stimulating factor, and congenital neutropenia is associated with severe immunodeficiency in humans. Neutrophils have three primary effector functions: phagocytosis, generation of oxidative bursts via ROS-dependent mechanisms, and antimicrobial proteins such as lysozyme, lactoferrin, cathepsins, and defensins that are either released intraphagosomally (phagocytosis) or exocytosed into the extracellular space (degranulation).

Neutrophils produce a variety of inflammatory and anti-inflammatory molecules, which are primarily released through their four distinct granule types [2]. Primary granules, also known as azurophilic and peroxidase-positive granules, contain powerful hydrolytic enzymes such as Myeloperoxidase (MPO), Neutrophil Elastase (NE), proteinase, various types of defensins, cathepsin G, azurodicin, vitronectin, and a variety of other bactericidal and endotoxin- While primary granule enzymes are primarily responsible for killing, digesting, and removing ingested microorganisms, secondary granules are specific, peroxidase-negative granules that contain substances that may have regulatory functions outside the cell. Lactoferrin, collagenases like Matrix Metalloproteinase 1 (MMP-1) and MMP-8, Lactoferrin, Neutrophil Gelatinase-Associated Lipocalin (NGAL), NADPH oxidase (NOX), M-ficolin, cysteine-rich secretory protein, cathelicidin LL-37, and lipocalin are examples of these common effector molecules.

Tertiary granules have overlapping contents with secondary granules, but they are mostly made up of Extracellular Matrix (ECM) degrading proteins like MMP-2 and MMP-9. These granules also contain leukolysin, arginase 1, and flavocytochrome b558. Mature human neutrophils also have easily mobilizable secretory vesicles that can be distinguished in function from azurophilic, specialised, and tertiary granules. These secretory vesicles store preformed cytokines and deliver proteins to the cell surface necessary for cell adhesion, such as integrins, as well as alkaline phosphatase and proteases, to aid transmigration and immune protection. As a result, neutrophils and neutrophil-derived molecules represent a plethora of potential biomarkers in cardiovascular diseases, which can be used to improve diagnosis, prognosis, and therapeutic options in the future.

Environmental risk factors

Abdominal aortic aneurysm is a specific, localised form of atherothrombotic disease that shares the same risk factors as occlusive atherothrombosis, such as male sex, ageing, possible genetic susceptibility, and dyslipidaemia. The observed progressive physiological enlargement of the aorta and the increase in pulse wave reflection associated with aortic rigidification influence AAA development. AAA patients have larger peripheral arterial diameters than age- and sex-matched control subjects. Smoking is the leading cause of AAA, which is most likely due to its ability to oxidise 1 antitrypsin. As a result, plasma nicotine could be used to monitor smoking in AAA patients [3].

The most sensitive predictor of AAA is a low level of high-density lipoprotein. This may be related to the effect of hypercholesterolaemia on the first stage of atheroma in the aorta, as well as the low levels of 1-antitrypsin conveyed by high-density lipoprotein in human AAA. Diabetes, unlike occlusive atheroma, is not a risk factor, most likely because glycation of extracellular matrix molecules increases their resistance to proteolysis. A patient's presence of AAA is a marker of atherothrombotic disease elsewhere,and aortic diameter is a predictor of total and cardiovascular mortality.

Neutrophil-to-lymphocyte ratio

The Neutrophil-To-Lymphocyte Ratio (NLR) has been used as a subclinical inflammatory marker and has recently emerged as a useful predictor of malignancy, prognosis in the coronavirus disease 2019 (COVID-19), as well as cardiovascular risk and adverse outcomes. A recent study looked at the role of NLR as a prognostic marker for AAA rupture. The average NLR was found to be significantly higher (9.3 vs. 3.39) in the patient group with ruptured AAA, and an NLR >5 indicates a 5-fold increased risk of AAA rupture. Furthermore, regardless of whether the AAA is ruptured or intact, AAA patients with NLR values greater than 5 have significantly worse outcomes in terms of 30-day mortality after OSR .

It has also recently been reported that the preoperative NLR is a good long-term predictor of postoperative outcome after EVAR. In fact, AAA patients with elevated NLR before surgery have a significantly higher 5-year mortality as well as significantly higher 30-day, 1-year, and 5-year reintervention rates after EVAR. A meta-analysis of 4066 enrolled patients with aortic disease, including AAA, confirmed the positive association of an elevated NLR with AAA disease, higher aneurysm rupture risk, increased cardiovascular risk and mortality, and higher postoperative reintervention rates. Indeed, it is unclear, and it has not been published in the current literature, whether the NLR can predict AAA growth.

lipocalin associated with eutrophil gelatinase

NGAL, a neutrophil-derived protein, has recently been the subject of research in a variety of diseases and appears to be a promising marker for the development and progression of AAA [4]. At the inflammatory site, neutrophils, as the primary source of NGAL expression, promote the formation of NGAL/MMP-9 complexes, and thus NGAL protects MMP-9 from proteolytic degradation and enhances its enzymatic activity. It was discovered that NGAL/MMP-9 complexes were present in the ILT, interface fluid, and aneurysm wall. If the NGAL/MMP-9 complexes were normalised to tissue weight and total protein concentration, the highest concentration was found in the luminal part of the thrombus (compared to the abluminal and central ILT layers, aneurysm wall, and interface fluid) [4].

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