Hypothesis

The Important Role of the Lymphatic System and Mast Cell Involvement in Nutcracker Syndrome and other Abdominal Vascular Compression Syndromes

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Abstract: Sufferers of Abdominal Vascular Compressions Syndromes (AVCS), including Renal Nutcracker Syndrome, present with a wide range of symptoms, not all of which are currently understood. Surgical outcomes vary and sometimes multiple compressions are present. Past research has shown that occlusion of the renal vein can increase venous pressure, thus increasing interstitial pressure, which initiates a transfer of fluid to the lymphatic system. If this pressure increase is chronic, the abdominal lymphatic system must assume the extra burden of this fluid transfer. The compression of any vein also implies an effect on the blood flow velocity and sometimes direction. This can cause blood endothelial cells to release mediators that can activate mast cells situated close to the vein wall. The mast cells then degranulate and release other mediators, causing an inflammatory cascade. The implications of this process are numerous, including damage to the vein itself (vein walls and endothelial cells), release of pro-inflammatory markers, damage to the extra-cellular matrix, angiogenesis and neolymphangiogenesis, and increased volume transfer to the lymphatic system. The increased burden on the lymphatic system has wide-ranging implications, given that the abdominal lymphatics are highly inter-connected within the pelvis, abdomen and thorax, and that mast cell mediators spread throughout the body to affect it systemically. The author proposes that these factors could explain the wide-ranging pain and the interplay of symptoms seen in AVCS patients.

Keywords: Abdominal Vascular Compression Syndromes; Nutcracker Syndrome; Mast Cell Activation; May-Thurner Syndrome; angiogenesis; neolymphangiogenesis; inflammatory cascade; Ehlers-Danlos Syndrome;

1. Introduction/ Background

1.1 Abdominal Vascular Compression Syndromes and consequent venous damage

There are several Abdominal Vascular Compressions known to cause localized pain and other symptoms in patients; these include compression of the left renal vein (Nutcracker Syndrome (NCS)), compression of the iliac vein(s) (May-Thurner Syndrome (MTS)), and compression of the celiac artery (Median Arcuate Ligament Syndrome (MALS)) [1]. These syndromes have been connected with a wide range of symptoms, including localized pain, nausea [2], vomiting [3], headaches [4, 5], and many others that are typically found comorbid to these conditions [6, 7]. Whereas previously defined as rare, more evidence is coming forth to suggest that they may be present in a greater sample of the population than previously thought [8].

All of these compressions, especially those of the veins, cause reduced flow velocities upstream of the compression, including reverse flow patterns (reflux) [9, 10, 11]. Reduced flow velocities have been shown to trigger endothelial cell dysfunction and damage due to reduced shear stress on the vein walls [12]. The reduction in shear stress and resulting dysfunction cause a number of different reactions, including the release of vein-dilating substances which lead to insufficiency in the veins, and subsequently, the veins to become varicosed. When Abdominal Vascular Compression Syndromes (AVCS), specifically NCS and MTS are present, this process leads to Pelvic Venous Insufficiency (PVI)[13], just as a similar process of refluxing blood flow in the legs is well understood to lead to Chronic Venous Insufficiency (CVI) [14]. The detailed mechanisms of this process will be discussed further in the following sections.

1.2 The Lymphatic System

Running often side by side with many of the venous vessels, the lymphatic system comprises of open-ended capillary beds, vessels, lymph nodes (LNs) and other structures. The principle function of the lymphatic system, other than immune system functions, is to transport fluids, solutes and cellular debris away from tissue. These substances are transported from the interstitial space and back into the circulatory system, via the lymphatic system. Lymphatic system dysfunction has been connected to many inflammatory diseases, including fibrosis of the heart and lungs, diseases of the gut such as Irritable Bowel Syndrome (IBS) and Ulcerative Colitis (UC), and joint disease such as Rheumatoid arthritis [15].

It is important to note that if the lymphatic system is continuously taking on the burden of increased interstitial fluid due to increased venous pressure, a similar process of lymphatic vessel and lymphatic endothelial cell (LEC) damage can occur, inducing lymphangiogenesis and lymphatic system dysfunction [15].

1.3 Mast Cells

Mast Cells (MCs) are hematopoietic cells that originate in the bone marrow and are then transported via the vascular system and distributed around the body. Recent studies have shown that MCs are present in nearly all vascularized organs [16], including the kidney and the brain (brain side of the blood-brain barrier (BBB)), as well as being extremely present in any context where the outside environment can come into contact with the body (e.g., the skin, respiratory and intestinal tracts) [16]. MCs often reside right at the boundary of vascular vessels and are thus poised to have a huge impact on the vascular system [17, 18].

MCs react to a wide-range and numerous quantities of substances in different situations. Upon activation, MCs immediately release the contents of pre-stored granules containing a number of inflammatory mediators (including histamine, heparin and a number of cytokines, as well as other mediators); there are also “de novo” mediators released a short while after. The consequences of the release of these mediators are not restricted to allergy (the best-known process being IgE), but are heavily involved in vascular tone, permeability, and angiogenesis as well as promoting movement of MCs and other leukocytes throughout different tissues types [19]. Recently, MCs have also been shown in high density near lymphatic vessels, and are being shown to cause similarly far-reaching effects on the lymphatic system as they do on the vascular one [16].

Prolonged increased venous pressure and reflux, such as that found at the sites of vascular compressions, can cause endothelial dysfunction that triggers the release of pro-inflammatory markers, namely through Mast Cell Activation, which then generates an inflammatory cascade. A more in-depth description of these processes will be given in the following sections.

In this paper, I bring together the findings of research done in the area of lymphatics (particularly those of the renal system), Mast Cell Activation, as well as clinical and anecdotal information on AVCS, to form a hypothesis on the possible cause of many unexplained symptoms and phenomena seen in AVCS patients. I propose that the interplay of excess lymph caused by increased venous pressure, the interconnectivity of the lymphatic system, and the effect of mast cells and their inflammatory actions all contribute to the multitude of symptoms and the disease progression seen in sufferers of AVCS.

2. Discussion

2.1 Concept of Interconnectivity of Abdominal Lymphatics

Kidneys have been shown to have an abundance of lymph vessels, suggesting that the role of lymphatics in proper kidney function is important [20]. Kidney lymphatics have been shown to be connected to many different LNs, far beyond the immediate region of the kidney. These include the aortic and caval groups of LNs [21], including the peri-aortic nodes consisting of the preaortic (celiac), paraaortic, and retroaortic nodes. Apart from those of the kidney, the paraaortic and retroaortic LNs also receive the efferents of the suprarenal glands, the common iliac vessels, (and thus efferents from areas of the pelvis and groin), the sexual organs, and the abdominal walls and lumbar veins. Different groups of LNs can be widely interconnected and there is free flow between groups, as unfortunately seen in the metastasis of cancerous cells to other organ systems via the lymphatic system (e.g., in the case of colon cancer). The connections are highly individualized and rarely identical from one person to another [21].

The kidney has even been seen to be directly connected to the celiac and iliac LNs. Also, renal lymphatic vessels have been seen to connect directly to the Thoracic Duct, and this at the level of the diaphragmatic crura and along the sympathetic nerves, but also sometimes passing between the crura to join at a more superior position within the mediastinum [21]. It has been postulated that these direct connections to the thoracic duct may also explain the presence of chyluria in some cases where lymphatic vessel insufficiency occurs, or even the occurrence of chyloperitoneum [21].

The extensive connectivity of the renal lymphatics and the individuality of connections in each case have significantly complicated attempts to measure the total renal lymph flow rates [22].

It should be noted that the majority of these abdominal and thoracic LNs are not readily palpable in clinical examination. Recent advances have occurred in new methods to better visualize the interconnectivity of the lymph vessels and structures (e.g., renal interstitial contrast injection for lymphatic system imaging [20]), but these are still rarely used outside of a research setting. Therefore the individual lymphatic connectivity of most patients remains unknown during investigation and treatment.

2.2 Transfer of fluid from the Venous to the Lymphatic System

In the lymphatic system of the kidney, interstitial fluid flows freely from interstitial spaces into the lymph vessels and onwards towards LNs according to the hydrostatic or oncotic pressure gradients present. Contrary to other tissue such as subcutaneous muscle, renal interstitial pressure is positive, which results in a relatively high normal lymph flow [20].

It has been shown that blockages to the venous flow of the small intestine can cause accumulated fluid to be shunted to the lymphatic system, leading to inflammation [23, 24]. A similar mechanism can occur where there are other blockages, for example at the site of renal vein compression, thus causing an increase of fluids transferred to the lymphatic system and an increase in lymphatic pressure [25]. The lymphatic system has been labeled by some as the "safety valve" of the kidney, and takes excess fluid away from it to prevent high intrarenal pressures, if the urinal or venous vessels are blocked [26]. Experiments done by occluding the renal vein showed an increase in interstitial pressure followed by a corresponding increase in lymphatic flow a couple of seconds later, and with this increased flow continuing some seconds after the vein was released [27]. Increased lymphatic flow has also been shown with partial vein occlusion [28]. In fact, increased lymphatic pressure believed to be caused by increased pelvic pressure was actually found to be caused by intra-renal increased pressure due to the venous connection between the kidney and the pelvic region [29, 30].

Increased lymphatic flow due to increased venous pressure can cause damage to lymphatic vessel structures through over-dilation (e.g., the over-dilation can result in incompetent valves) [31], and this may have consequences for patients who have suffered an occlusion of the vein and thus localized increased venous and lymphatic pressure over a period of time. Any dysfunction of the surrounding lymphatics may have effects on kidney function over time (e.g., proteinuria, elevated serum creatinine, etc.), including possible renal interstitial fibrosis due to unabsorbed renal interstitial edema [32]. In particular, it has been shown that increased venous pressure can show a disproportionate increase in lymphatic protein levels [33]. Although lymphatic protein levels are not themselves commonly monitored in a clinical setting, this may correspond with the findings of proteinuria, which, interestingly, is commonly found in NCS sufferers [34, 35], given that the compression of the renal vein causes localized increases in blood pressure, inducing an exchange of fluid to the lymphatic system

Similarly, if lymph vessels run adjacent to the main vascular vessels, it is plausible to imagine that compression of a vascular entity by a structure such as another vascular entity, an organ or bone, could also cause a compression in the lymph vessel, causing an increase in local pressure and subsequently localized edema in the abdomen or pelvis.

2.3 Mechanisms of Venous Insufficiency

As previously mentioned, venous compression causes an increase in the localized blood pressure and reduction in the flow velocity in the veins prior to the site of the compression. Blood can effectively stagnate and can even reverse the direction of the flow (reflux). Endothelial cells (ECs) lining the walls of the veins can sense the change in shear stress that occurs as blood flow velocity drops and even reverses. In healthy ECs, changes to the laminar shear stress trigger the release of vasoactive and anti-inflammatory substances, such as Nitrous Oxide (NO) and Prostacyclin (anti-inflammatory in the vascular

setting) [33]. However constant exposure to reduced shear stress and increased wall pressure damages the ECs and causes dysfunction, including the reduced expression of anti-inflammatory substances and an increase in pro-inflammatory ones such as free radicals, and also liberating signaling molecules for transactivation factors.

Where venous wall pressure is continuously high, it has been found that venous wall undergoes remodeling, creating a wider and more tortuous vein [33]. These varicose veins have a proliferation of unhealthy ECs, but also Smooth Muscle Cells (SMCs) which contribute to the lack of venous tone. There is also a down-regulation of vasoconstricting agents, and up-regulation in vasodilators, including a marked increase in the endothelial inducible NO synthase (iNOS) in particularly tortuous areas, probably contributing to their dilation.

2. 4 Role of Mast Cells and the Inflammatory Cascade

Recently there have been advances in the understanding of ECs and their interaction with leukocytes, namely Mast Cells (MCs), and the creation of an inflammatory cascade. Mast Cells have been shown to be positioned right at the walls of venous and lymphatic structures [36]. Mast cells release many vasoactive mediators that create both localized and systemic effects that can vary spatially and in time. The vascular and lymphatic systems act as conduits to disseminate MC mediator signaling during inflammatory episodes. These mediators are released in response to stimuli in two phases: the first being an almost immediate release of pre-stored "granules" containing many mediators (degranulation), and the second being the relatively slower release of newly synthesized (de novo) mediators that can last over a substantial period of time. These phases can have an additive effect, meaning that the effects created by the mediators released in the second phase can add to and compound the effects of the mediators from the first phase.

Venous flow reversal and reduced shear stress has been shown to trigger MC activation [33]. Inflammatory mediators such as cytokines are released, including Transforming growth factor β1 (TGF-β1), tumour necrosis factor-α (TNF-α) and interleukin-1 (IL-1), which have all been found in varicose veins. Also MCs are induced to congregate on the vein wall and valve endothelium. Table 1 shows some of the better-known mediators released by MCs and their effects on the vascular and lymphatic system.

Mast Cell Mediator	Effect on Vasculature	Effect on Lymphatics
Histamine	- Activates H1 receptors on ECs increasing endothelial permeability and gaps between ECs. - Causes calcium flux in ECs which ultimately can cause smooth muscle relaxation and thus vasodilation. - Triggers the release of EC stored mediators (Von Willebrand Factor (VWF), P-Selectin, IL-8, etc.).	- Increased fluid transfer to extracellular space creating more lymphatic efferent - Increased cytokines released require removal and transportation

	- Can stimulate Platelet Activating Factor (PAF) in ECs - Possible involvement in angiogenesis	
Tryptase	- Can increase leukocyte rolling and adhesion - Can stimulate PAF in ECs - Can increase response to TNF-α triggered IL-6 production by ECs - Promotes breakdown of the Extra Cellular Matrix (ECM) and fibronectin, potentially causing SMC apoptosis. This could cause atherosclerosis.	- Can be involved in the creation of Matrix Metalloproteinases (MMPs) which can cause ECM degradation causing possible changes to LEC junctions
Chymase	- Believed to have a role in angiotension creation and thus vascular tone - Promotes breakdown of ECM and fibronectin, potentially causing SMC apoptosis. This could cause atherosclerosis. - Can be involved in the creation of MMPs, which can cause ECM degradation and angiogenesis	- Can cause direct and indirect ECM degradation and creation of MMPs, causing possible changes to LEC button junctions
Heparin	- Key reaction is with antithrombin III to prevent thrombosis - Binds growth factors and cytokines to it, potentially aiding them to be transported distally into tissue	- May affect lymph system contractility
Tumor Growth Factor (TGF-β)	- May promote angiogenesis	- Can cause lymph node fibrosis
Tumor Necrosing Factor (TNF-α)	- Rapidly increases permeability and thus can causes rapid hypotension - Induces activation leukocytes and adhesion to ECs - Promotes prostaglandin production - Immediate but also potentially persistent effects after MC activation - May promote angiogenesis	- Promotes Lymph Node enlargement during immune response
Leukotrienes (LTC4, LTD4, LTE4)	- Believed to enhance and prolong the effects of histamine -Increase vascular permeability - Cause calcium flux in ECs	

Platelet Activating Factor	- Produced by several cell types including MCs and ECs - involved in anaphylaxis (hypotensive and other) - Induces leukocyte recruitment - May induce MC degranulation and so cause an increased localized and systemic response	
Prostaglandin PLD2	- Suspected to cause increased vascular permeability and vasodilation - Inhibits platelet formation - Seems to inhibits certain leukotrienes and promotes others	
Interleukin 1 (IL-1)	- Promotes lymphocyte adhesion to ECs - Stimulates pro-coagulant activity near ECs	- Inducer of Lymphocyte-Activating Factor (LAF)
Interleukin 6 (IL-6)	- Affects endothelial barrier function - May promote lymphocyte adhesion	
Interleukin 8 (IL-8)	- Can cause rolling, activation and diapedesis of MCs into post-capillary venules	
Vascular Endothelial GF (VEGF)	- Promotes angiogenesis - May permit increased EC junction permeability in some cases	- Promotes lymphangiogenesis - May permit increased LEC junction permeability in some cases and close junctions in others

[15, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46]

Table 1. A list of mediators released by Mast Cells that have an effect on the vascular and lymphatic systems.

This list may not be comprehensive for all mediators and effects. There are less effects listed for the lymphatic system, however this does not mean that there is no effect as such, but moreover it is a consequence of the fact that this area of MCs effect on the lymphatic system has only recently begun to be studied in earnest.

Previously, it was generally put forward in the medical community that Chronic Venous Insufficiency (CVI) was caused by incompetent vein valves that failed somehow in their function and thus let blood slip backwards in the vein. However, more recent research has shown that vein walls over-dilate prior to venous valve failure, which then

causes more stagnation followed by more dilation and so on, in a negative consequence feedback loop [33]. In effect, it is the drop in laminar shear stress due to reduced velocity and refluxing that triggers the vascular ECs, and their activation of MCs and subsequent release of the inflammatory agents, which over time causes further damage to the vein walls and exacerbates the dilation and tortuosity of the veins. Thus the endothelial cell – mast cell relationship under abnormal venous flow seems to be an important factor in the progression of venous insufficiency.

Another factor critical in the discussion of vascular effects of MCs is the release of different growth factors and other growth-inducing mediators. For example, vascular endothelial growth factor (VEGF) in its different forms (among other mediators) has been shown to be extremely important in angiogenesis and lymphangiogenesis [23, 36]. Therefore MCs are not only involved in remodeling of existing veins, they are responsible for triggering the production of new venous and lymphatic structures at inflammatory sites.

MCs release many mediators which can affect, among other things, SMCs, increasing vascular dilation. Some of these mediators act directly on the ECs to open EC junctions and increase the permeability of the veins. In turn, substances released by the ECs encourage up-regulation of adhesion factors in leukocytes, that then release their granules (Weibel-Palade bodies (WPBs)), which encourage MC rolling and extravasation [36]. Heparin is also released by MCs, ensuring increased blood flow throughout the area. This compromised barrier function of the ECs could be created so the MC discharged mediators and recruited particles can be dispersed more efficiently through the vascular and lymphatic system, thus creating systemic reactions.

A summary of these effects can be seen in Figure 1.

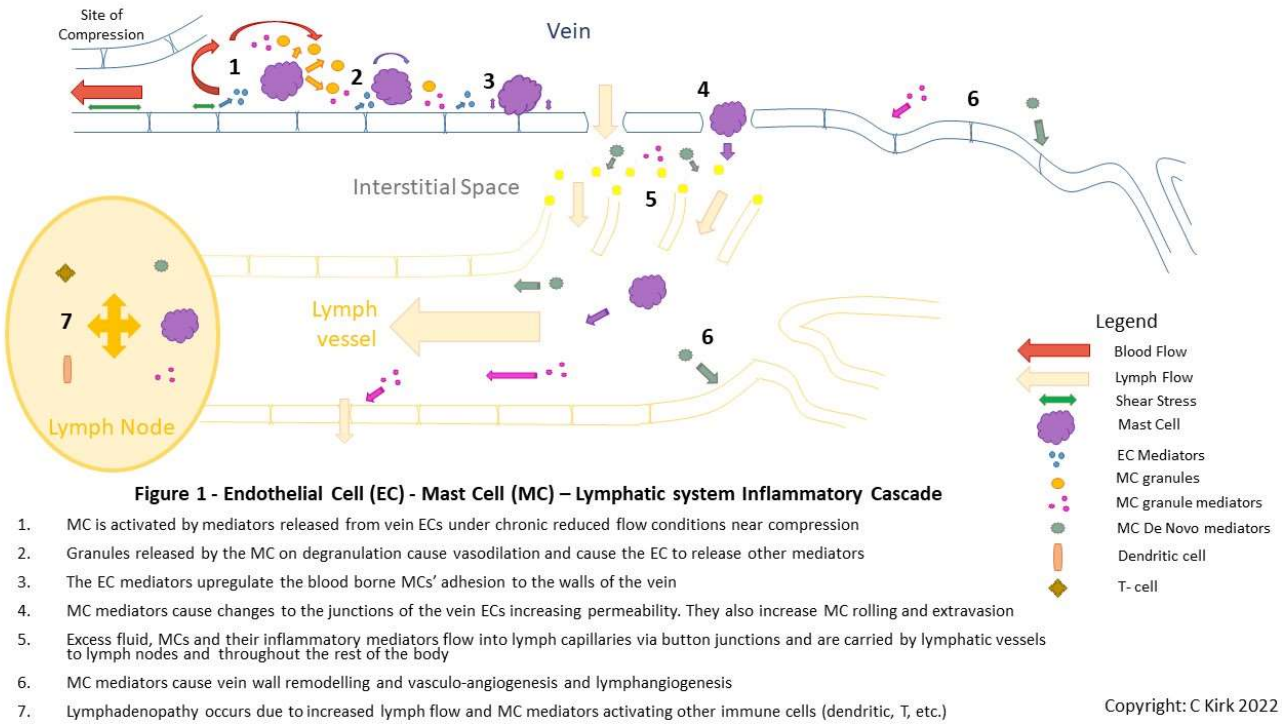

Figure 1 - Endothelial Cell (EC) - Mast Cell (MC) – Lymphatic system Inflammatory Cascade

Figure 1 shows that just anterior to the compression, blood flow velocity decreases and thus laminar shear stress at the wall of the vein EC is reduced. This triggers the ECs which release mediators which then trigger MCs situated near the vein wall. The MCs degranulate, immediately releasing a plethora of highly reactive mediators, including histamine, tryptase, chymase, etc. These cause vasodilation, among many other effects. The ECs are themselves re-stimulated by these mediators and release WPBs containing mediators which encourage MC rolling and adhesion to the vein and valve walls [36]. P-selectin released from the WBP causes changes to the junctions between ECs and increases permeability. This allows more fluid to pass into the interstitial space as well as MC extravasation. As well as the mediators released on degranulation, de novo mediators are also released causing other inflammatory effects, including effecting permanent changes to the vein wall and causing angiogenesis. All mediators can also pass into the interstitium, and the fluid, mediators and MCs can all pass into the lymph system through the lumina and button junctions in the lymph capillaries. The additional fluid from increased venous pressure and from the increased permeability causes high lymph volume. This flows through the highly interconnected lymph network to LNs all over the abdomen, thorax and pelvis depending on the highly individualized connections specific to the particular body. Lymphadenopathy occurs dues to the increased flow volume and also in reaction to the MC mediators present in the lymph. Other immune responses, such as the release of dendritic and T-cells, may occur in response. These mediators and immune cells continue to be transported throughout the lymph system until they pass into the vascular system at the thoracic duct. From there they can pass throughout the body and can have effects distally and systemically. The effects of certain mediators can also create changes in the lymphatic system such as lymphangiogenesis, and effects on lymphatic EC junction permeability.

2.5 Changes to the Lymphatic System

The lymphatic system plays an important role not only for the body's immune response (lymph is filtered and monitored for pathogenic invaders), but specifically for mast cells which use the lymph vessels to transport their mediators to affect systemic responses. It has been shown that pathological changes to the venous system can cause microangiopathic changes not only in the vascular network, but also in the lymphatic network [47].

When lymphatic function is lost, or when there is undue pressure on the lymphatic system due to increased lymph volume, edema can occur. This is commonly seen in CVI of the peripheral limbs, but is hardly ever considered for venous insufficiency in the abdomen or pelvis. As discussed, excess venous pressure can cause transfer of fluid to the lymphatic system. Also, as discussed in the following section, acute changes to vascular permeability caused by the effects of mast cell mediators can cause increased fluid to pass into the interstitial space and can cause localized edema [47]. In order to avoid edema, the lymphatic system must increase lymphatic flow. This is conjected to be the main buffering system to prevent edema forming.

Clinical skin sampling of patients with peripheral CVI has shown morphological changes to the lymph system including collapse of the lumina, intracellular junction damage, and damage to the filaments which anchor the lymphatic vessel and keep it open [47]. Damage was also seen to the LECs and the muscles surrounding the lymphatic vessels. Any process causing dilation and changes to the contractile muscles of the lymphatic vessels will have an important effect on the proper function of those vessels. This is evidence that similar changes as those seen in the venous system in CVI, also occur in the lymphatic system, and that these can cause lymphatic system dysfunction.

New lymphatic vessel formation (neolymphangiogenesis) is often stimulated by VEGFR-3/ VEGF-C, and is believed to be a protective response in order to deal with edema and pro-inflammatory substances [48]. Cytokines released by MCs during activation can result in the release of VEGF-C and D.

LECs can express proteins that can modulate cytokines, and make them transportable. Therefore lymphatic vessels play an important part in the regulation of both local and systemic inflammatory processes.

Neolymphangiogenesis has been shown to occur concurrently with different kidney diseases, with markers such as VEGF-C also found to be present in these cases [48]. The increased production of lymphatic vessels may help with removal of excess fluid from the stressed kidney and thus reduce edema. However the presence of more vessels might increase the immune response against the kidney, resulting in greater inflammation and damage.

2.6 Endothelial Junctions

As discussed, both vascular and lymphatic vessels are lined with endothelial cells. These cells are connected by cell-to-cell junctions. Blood Endothelial Cell (BEC) junctions fall into 3 types expressing mainly one mediator: adherens junctions (that express VE-Cadherin); tight junctions (that express claudins); and gap junctions (that express connexins) [49]. These vascular junctions are involved in many processes such as vasculo- and angiogenesis, vessel leak and leukocyte extravasation.

The LEC junctions are organized into 2 types: button and zip. These junctions reflect the unique functionality of the lymphatic vessels. The button-like junctions or "buttons" are positioned to have a very open structure and allow free ingress of fluid from the interstitial space to prevent edema without junction dissolution. They are actually located between small flaps over lumina that are held open by small fibres. They are principally found at the end of the lymphatic capillary vessels. It is thought that leukocytes also pass through these junctions to enter the lymphatic system, although this is most probably mediated by the leukocytes themselves.

The fibres which hold open the flaps are made of emilin-1 and fibrillin and serve to anchor the lymphatic capillaries to the surrounding extracellular matrix (ECM) [50, 51]. As the interstitium fills with fluid the ECM expands and these fibres are stretched, pulling on the flaps to allow the fluid to freely enter the lymphatic capillaries.

The zip-like or "zippers" are tight junctions that prevent fluid from passing through. These typically line all the lymph vessels transporting the lymph away from tissues and throughout the lymphatic system. They ensure that the vessels maintain low fluid loss so they can effectively transport the lymphatic fluid.

Although this is a fairly new area of research, it seems that VE-Cadherin also has an effect on LEC junctions as well as BEC junctions. While it seems to increase the permeability of BEC junctions permitting greater fluid egress into the interstitial space along with leukocyte extravasation, in LECs it appears to encourage the closure of the flaps in buttons as well as the opening of the zippers [52]. This means that less fluid is drawn into the lymph capillaries, and lymph can leak out of transport vessels, effectively causing localized edema in the former and potential chyle ascites in the latter. Inflammatory mediators may cause reversal of junction type in LECs, encouraging the transformation of zipper junctions in the transporter vessels into permeable button junctions, and the button junctions to close and become tight at the capillaries [49, 52]. These mechanisms may be implicated in conditions such as lymphedema, but require further study.

2.7 Connections to Connective Tissue Disorders (e.g., Ehlers-Danlos Syndrome)

There may be some mechanism in connective tissue disorders promoted by mastocyte activation that induces the fibrillin-rich anchoring fibres to become more lax and less effective at holding the flaps open at button junctions, reducing their permeability and ability to uptake fluid and prevent edema. As shown in Table 1, MCs liberate many mediators including tryptase and chymase. It has been shown that fibrillin and microfibrils are highly susceptible to degradation by tryptase and matrix metalloproteinase-9 (MMP-9) [39]. The MMP family is highly capable of degrading all elements of the ECM, while tryptase can also degrade fibronectin. Chymase, when released during mast cell degranulation, activates pre-molecular forms of MMPs, which result in the creation of activated MMPs including MMP-9. As well as or perhaps due to being involved in ECM degradation, MMP-9 has been linked to many inflammatory diseases including aneurysms, inflammatory gastrointestinal (GI), hepatic, atopic diseases, acute pancreatic failure, and rheumatoid arthritis [37]. Some of these conditions themselves are linked to Connective Tissue Diseases (CTDs) such as Ehlers-Danlos Syndrome (EDS) [53, 54], which is often comorbid with Mast Cell Activation Syndrome (MCAS) [55, 56].

In many CTDs, diffuse lymphadenopathy is seen [57]. Sometimes mesenteric lymphadenopathy is the only manifestation of lymph node involvement and, as these are hard to manipulate clinically, they are not discovered unless they appear large enough to be visible on any CT or MRI scans. Lymphadenopathy in CTD sufferers have also been found

at other sites of the body (thorax, neck, axilla, inguinal regions, etc.). Similar lymphadenopathy has been noted anecdotally by AVCS sufferers, with and without CTD diagnoses.

2.8 Negative Feedback Loop of Inflammation

As discussed in this paper, MC mediators can have a profound effect in remodeling the vein wall, causing dilation of the vein which can then lead to malfunctioning of the vein valves. The same processes may even apply to the lymphatic vessels but this needs further investigation. The widening of the veins and the increased tortuosity due to the remodeling process will act to further reduce blood flow velocity and increase turbulent flow and reflux. So the MC activation adds to the worsening of the condition in this way also.

Exterior MC activation triggers may have a considerable role in worsening the symptoms of AVCS due to the inflammatory cascade and its effects on the vascular and lymphatic systems. Figure 2 is a simplistic representation of the possible effects of MC triggering that can provide a negative feedback loop to worsen a vein compression.

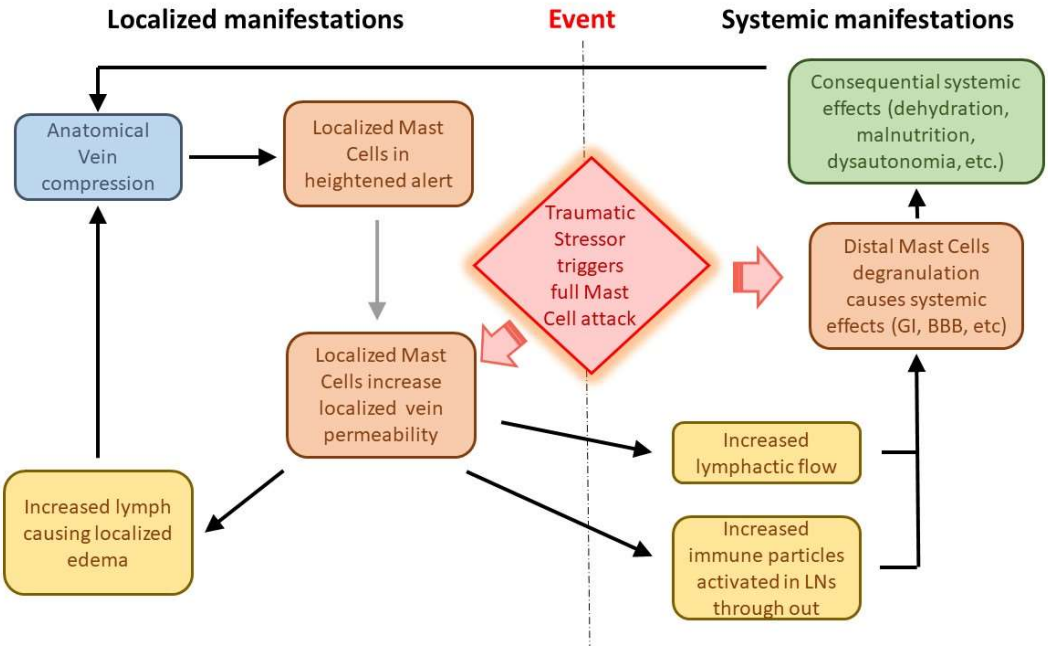

Figure 2. Cyclic involvement of Mast Cells and lymphatic system in vein compression and symptoms

If a vein compression exists, localized MCs are in a sensitized state given the increased endothelial shear stress and subsequent release of mediators from ECs. Due to a percentage of local MCs degranulating, symptoms will be mainly localized with perhaps some mild systemic effects. However, if any "traumatic" stressor is introduced (accident, injury, infection, serious emotional stress, etc.), we know severe MC activation

can occur at a systemic level [58, 59]. This systemic level MC activation will affect the lymphatic system locally, causing changes to the vascular and lymphatic systems including vein wall and junction remodeling leading to increased permeability and damage to lumina. This may cause localized edema in the abdomen and pelvis. This localized edema could actually accentuate pressure on surrounding veins, thus increasing venous pressure and creating increased compression and more venous reflux. The systemic effect on the lymph system (e.g., increasing LN response, increased lymph flow) plus the consequences of systemic MC symptoms such as nausea, vomiting, etc. on body hydration levels and other factors, can also cause the compression to increase, thus increasing the localized MC response and again the systemic one, and so forth, continuing the vicious circle of inflammation.

3. Hypotheses

Abdominal Vascular Compression Syndromes can cause pelvic and abdominal venous insufficiency, both of which are subject to the same mechanisms as peripheral CVI. Due to the compression, blood flow velocity is reduced upstream anterior to the compression, and causes increased localized venous pressure. The reduced blood flow velocity causes reduced shear stress on the blood endothelial cells, triggering a process causing mast cells on the boundary of the vessel to degranulate and release their inflammatory mediators. The mediators released cause localized remodeling of the vein (permeability changes, dilation, valve failure, tortuosity; in short varicosis), as well as triggering angiogenesis. The mediators also have an effect on the local lymph system (permeability changes, possible LEC junction changes, influx of leukocytes, activation of LNs, lymphangiogenenis).

The increased venous pressure causes increased lymphatic flow through transmission of fluid through the interstitium. This increased lymph volume flows through a very individualized network of lymph vessels interconnected to many pelvic, abdominal and thoracic LNs. Lymphadenopathy can occur due to increased lymph and from the MC cytokine mediators and immunological information transported within the lymph from the site of MC activation. This can cause pain distally from the site of the compression, and, as many of these LNs are not readily palpable in the abdomen/ thorax/ pelvis, may go unspecified as such. Also the perceived distance and non-connectedness from the compression site may lead to a non-specific diagnosis. This may also explain why some NCS patients have right-sided abdominal pain, when the compression is actually slightly on the left.

I propose that the interconnectivity of the abdominal and pelvic lymphatic system may also explain why AVCS sufferers often suffer from more than one compression syndrome, because the increased lymph flow may affect other areas of the pelvis and abdomen adjacent to veins susceptible to compression. MALS symptoms may be increased due to the increased flow in the area of the diaphragmatic crura, just as MTS symptoms may be increased due to connections to pelvic LNs.

The increase in lymph volume arriving at the thoracic duct may create a subsequent increase in volume in the left subclavian vein, with potential increased pressure and thus dilation within the left internal jugular vein, giving clinical symptoms such as localized discomfort, bruising, pressure behind the left ear, and even subsequent left-sided pulsatile tinnitus. It may also create issues in the thoracic outlet, increasing the incidence of Thoracic Outlet Syndrome (TOS)-type symptoms in AVCS sufferers.

There are many physical and clinical symptoms noted which correlate with this hypothesis. In the case of NCS, surgeons who have operated on the kidney (auto, transplantation, nephrectomy, etc) have noted anecdotally that the kidney appears "tense" within its capsule, which could be a visual sign of the effects of the increased venous pressure. Also, patients that have been operated on for NCS and other AVCS have been investigated for Jugular vein compression and TOS, due to having the head, neck and shoulder clinical symptoms listed above.

The MC activation near the site of compression causes the release of mediators that are transported within the vascular and lymphatic systems throughout the body, therefore the effects of these mediators manifest themselves and are felt throughout as well. Patients with AVCS tend to present very often with unexplained GI symptoms such as a high level of nausea, vomiting, unexplained chronic constipation alternating with diarrhea, abdominal pain and cramping. They also experience pre-syncope, tachycardia, flushing, food and other sensitivities and extreme reactions to certain drugs. All of these symptoms have been linked to systemic MC activation.

I propose that MC mediators that cause angiogenesis, such as VEGF, are responsible for the considerable collateral vein formation that is seen in many AVCS patients that receive delayed diagnosis and treatment. The angiogenesis continues as long as the compression is present and blood flow is slowed, as the MCs are continuously being activated and releasing mediators. Certain of these new vein connections may help reroute the blood flow around the compression, but as these happen spontaneously in a non-directed fashion, sometimes the connections are made from larger veins to smaller veins that are not capable of assuming the increased blood flow of two returning systems. This can cause flow problems in the new veins or in the new organ system of that vein. For example, when collateral veins form from the renal vein to the ascending lumbar vein, increased cerebrospinal fluid pressure has been noted with a consequent augmentation in headaches [60]. There is most probably also significant lymphangiogenesis in these cases; however, this is not easily confirmed or comparable, due to the current difficulty in visualizing the lymphatic system, and also the limited research in this area. This may change in the future with more interest in the role of lymphatics in many disease progressions, and the adoption and availability of techniques such as contrast-enhanced ultrasound (CEUS), or near-infrared (NIR) fluoresence imaging for the lymphatic network [61, 62, 63].

The fact that the lymph system is active with additional flow and increased inflammatory mediators due to the MC activation may explain the predominance of GI symptoms seen in AVCS patients, because lymphatics play such an important role in function of the GI system. The GI system also contains a high concentration of mast cells which themselves could be triggered from the MC mediators that have been systemically released. It would be interesting to see if AVCS patients have an increased incidence of lyphangiogenosis in the GI region as well as near the sites of the vascular compressions.

It has been shown, for the GI system, that disruption or dysregulation of the lymphatics following injury, chronic inflammation or indeed surgery, appears to increase disease progression and morbidity [28]. These findings may well also apply to AVCS, in that the chronic inflammation results in undesired changes to the surrounding lymphatics. Surgery for AVCS, typically focused on correcting the vascular anomaly, may unfortunately damage surrounding lymphatics, causing further issues.

As well as due to vein compressions, blood flow is also slowed when there is stenosis after certain treatments (such as in certain cases of partial or complete stenosis found after Left Renal Vein Transposition (LRVT) [64]), and also in cases where the blood vessel remains deformed even after the source of compression has been removed (for example in some severe cases of MALS). In effect, the MC activation and its inflammatory and systemic effects would theoretically continue until the normal blood velocity is restored. It should also be noted that direction of flow seems important to ECs, so blood flow in a reverse direction via ovarian veins as seen in NCS, and particularly in Left Ovarian Vein Transposition (LOVT), may continue to stimulate MC activation, at least to some extent. The importance and interconnectivity of the lymphatic system in the pelvis and abdomen may also explain why even during successful surgeries for AVCS, lymph complications such as chyle leaks can occur and cause delayed healing.

The action of tryptase and chymase-activated MMPs may cause damage locally to the fibrilin fibres holding open the lumina of the lymph capillaries. As discussed, this may cause the junction to close, reducing the ability of the lymphatic system to transport away interstitial fluid, thus contributing to edema. The systemic effects of these connective tissue- attacking substances may explain the fact that many AVCS sufferers also show clinical signs of CTDs, including EDS.

There is interest in the interactions between MCs and other immune functions and nociceptor neurons. There appears to be a biochemical signalling dialog between the two, with MCs releasing the mediators previously discussed, and nociceptor neurons releasing neuropeptides [65]. Several MC mediators have been shown to directly stimulate and sensitize primary afferent nociceptors (PANs), triggering pain signals. Therefore the presence of MC mediators released due to the reduced velocity blood flow may be one of the reasons AVCS sufferers experience a high level of pain due to their conditions, the other being the presence of localized edema, which has long been accepted as causing pain, for example in the peripherals.

For certain inflammatory disorders, therapies based on limiting MC activation are being used or investigated. Most of these drug-based therapies either limit the activities of the pre-stored or de novo MC mediators (anti-histamines, anti-leukotrienes, anti-protineases, etc), or help prevent MC activation and the release of these mediators (MC stabilizers) [66, 67]. Whereas not a conclusive treatment as such in that the anatomical issue remains the same, perhaps the application of some of these therapies for AVCS sufferers may alleviate certain symptoms associated with or aggravated by MC activation.

4. Conclusion

In summary, I propose that due to the processes occurring consequent to venous compression, MC activation is triggerd and subsequent inflammatory cascades are created, and that AVCS sufferers show symptoms of such. This hypothesis can be proved by evaluating AVCS sufferers for systemic and localized MCAS symptoms, and by seeing if MCAS treatment provides relief. I also propose that the lymphatic system suffers an increased burden due to both the increased lymphatic volume induced by increased venous pressure, and the changes to the vascular and lymphatic systems

triggered by the MC activation. This theory can be investigated further by using lymphatic visualizing techniques, and collecting data on lymphadenopathy in AVCS patients. Finally it is suggested that any findings to support these hypotheses be used to help revise the current treatment techniques (surgical and other), to better promote successful treatment outcomes.

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