



Vasculitis

Introduction: Vasculitis, simply put, is blood vessel inflammation. But vasculitis is far from a simple subject. It is not one, but a multitude of diseases with a wide variety of manifestations, ranging from skin involvement alone to widespread life-threatening damage to multiple organs.

For the most part, the type of vasculitis encountered depends on the size of blood vessels that are inflamed. When inflammation occurs in a blood vessel, it can either become occluded, narrowed, or in the case of larger vessels may dilate. This process is responsible for the complications seen in various forms of vasculitis. While much overlap occurs in individual patients, these diseases can generally be divided into *small*, *medium*, and *large vessel* vasculitis.

There are many specific diseases that fall under the heading of vasculitis, but oftentimes blood vessel inflammation is identified yet a specific disease cannot be diagnosed. Included under the category of small vessel vasculitis are *leukocytoclastic cutaneous vasculitis (LCV)*, *Henoch-Schönlein purpura (HSP)*, *cryoglobulinemic vasculitis*, and *microscopic polyangiitis (MPA)*. Diseases considered forms of medium vessel vasculitis include *polyarteritis nodosum (PAN)*, *Wegener's granulomatosis (WG)*, *Churg-Strauss syndrome (CSS)*, and *primary angiitis of the central nervous system (PACNS)*. Finally, conditions that present as mostly large vessel vasculitis include *giant cell arteritis (GCA)* and *Takayasu's arteritis (TA)*. GCA is discussed in detail elsewhere (see Polymyalgia Rheumatica/Giant Cell Arteritis section).

The above diseases are considered *primary* forms of vasculitis, but a number of conditions are associated with what may be known as *secondary* vasculitis. Infections (HIV, hepatitis B or C, bacterial, fungal), cancers (leukemia, lymphoma, solid tumors), medications (PTU, hydralazine, antibiotics), and other rheumatic diseases (rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome) have all been associated with different forms of vasculitis. When vasculitis is identified, therefore, it is prudent to search for potential secondary causes, which can greatly influence how the patient is treated.

Features of Small Vessel Vasculitis: When we refer to small blood vessels, we are mostly referring to the *capillaries*, the tiny vessels not usually visible to the naked eye that supply blood to various parts of the body. The most common location for

involvement in a patient with small vessel vasculitis is the skin, but less commonly the small blood vessels supplying the nerves, kidneys, lungs, or intestines may become inflamed and potentially produce damage in these areas. Table 1 summarizes the key features of several types of small vessel vasculitis.

When the skin is involved, the typical finding is known as *purpura*, which appear as raised red or purple spots which may be anywhere in size from pinpoint to one inch in diameter. Skin ulcers, painful red nodules, and a lacy red or purple rash known as *livedo* are other findings that can suggest a diagnosis of vasculitis.

Inflammation of blood vessels in other organs can produce more serious complications. Nerve involvement can cause numbness or weakness in an arm or leg, known as *mononeuritis multiplex*. Patients with this complication most commonly have difficulty moving a hand or foot, known as “wrist drop” or “ankle drop,” respectively. MPA and cryoglobulinemic vasculitis are examples of conditions that can manifest in this way. Kidney involvement results in blood or protein in the urine and can impair kidney function. This is almost always unaccompanied by pain in the kidney region. HSP and MPA are often complicated by kidney involvement. Small blood vessels in the lung may be inflamed in MPA patients as well, causing damage to the lungs that may resemble pneumonia on chest x-rays. Intestinal involvement, seen in some patients with HSP and MPA, may result in bleeding or potentially perforation of the gut.

Table 1

<u>Type of Vasculitis</u>	<u>Major Manifestations</u>
LCV	Purpura, skin ulcers
HSP	Purpura, kidney and gut inflammation
Cryoglobulinemia	Purpura, nerve damage, loss of circulation to fingertips
MPA	Purpura, kidney and gut inflammation, nerve damage

Features of Medium Vessel Vasculitis: Medium-sized vessels are large enough to be called arteries or veins but not large enough to be given a name. Inflammation of such vessels typically causes loss of blood supply to the organ concerned and has the potential to cause severe damage as a result. Many conditions that are considered predominantly medium vessel vasculitis also have some small vessel inflammation (WG, CSS, and PACNS, for example), but PAN tends to be characterized exclusively by inflammation of this size of vessel. The key features of these forms of vasculitis are listed in Table 2.

The kidneys are a target for many forms of medium vessel vasculitis. In PAN, parts of the kidney may lose blood supply, and elevated blood pressure may occur as a result of involvement in this region. The kidney involvement in WG or CSS may also result in blood or protein appearing in the urine, sometimes progressing to loss of kidney function. Lung disease in PAN is generally absent, but it is common in WG, associated with cavities or nodules in the lung tissue, and seen in virtually every patient with CSS, associated with asthma. In WG, and less commonly in CSS, the sinuses, eyes, or trachea (“windpipe”) may become inflamed and damaged.

While less common in WG, involvement of the heart and intestinal tract may be seen in patients with PAN or CSS and result in life-threatening complications and damage. The brain is the exclusive target of PACNS, a rare condition resulting in strokes, headache, confusion, and fever. Other forms of vasculitis, however, can also involve the brain, including PAN and CSS, and these conditions can also cause damage to major nerves, as is also seen in small vessel vasculitis.

Table 2

Type Vasculitis	Major Manifestations
WG	Sinus, lung, and kidney inflammation
CSS	Asthma/lung damage, intestinal, kidney, and nerve inflammation
PAN	Kidney damage, elevated blood pressure, intestinal, heart, and nerve damage
PACNS	Strokes, headaches, confusion, fever

Features of Large Vessel Vasculitis: Because a description of GCA is included elsewhere (see Polymyalgia Rheumatica/Giant Cell Arteritis section), we will focus on TA, another major form of large vessel vasculitis. Even though both of these diseases affect similar blood vessels, they occur in different age groups, with GCA affecting older Caucasian adult and TA affecting mostly young Asian women. When vasculitis involves a “large” vessel, it is usually a vessel significant enough to be given a name. The aorta, the largest blood vessel in the body, and its branches are most commonly affected.

The most common finding when large vessels become inflamed is pain in the region that blood vessel supplies. While headaches and jaw pain are the most common features of GCA, patients with TA most commonly will have pain in an arm due to narrowing of its large blood vessels. This is aggravated when the patient uses the arm, a symptom known as *claudication*. Less commonly, when blood vessels leading to the brain become narrowed, dizziness, fainting episodes, and strokes may occur. When the aorta itself becomes inflamed, this vessel usually dilates and can result in heart murmurs and strain on the heart muscle.

The above manifestations may lead the physician to suspect vasculitis, but early in course of both TA and GCA, the only symptoms may be fever, weight loss, night sweats, and muscle aches. These findings are not specific enough to suggest the diagnosis until other findings emerge that raise the question of impaired blood supply or blood vessel damage.

Diagnosis: Ideally, if a diagnosis of vasculitis is to be made with confidence, inflammation of the blood vessels in question should be documented. The procedures required to diagnose vasculitis in this way may be complicated, but the investment in such efforts is wise considering the potential complications of undiagnosed and untreated vasculitis as well as the potential complications of therapy.

Any good evaluation begins with a review of the patient’s symptoms and physical examination findings. If some of the problems listed above are present, vasculitis may be

suspected by an experienced practitioner. Generally speaking, whenever unexplained fever and damage to any organ occurs, particularly when it would not be expected (a stroke in a young patient, for example), vasculitis must be considered.

Laboratory tests typically demonstrate elevations in markers of inflammation, such as the *sedimentation rate* and *C-reactive protein*. These tests, however, are also elevated in patients with a number of other inflammatory diseases and infections are not specific enough to make a diagnosis. Blood chemistry tests may suggest complications of vasculitis, such as impaired kidney function, and blood counts can show elevations in certain types of white blood cells involved in inflammation (particularly useful in patients with suspected CSS). When kidney involvement is suspected, the best method to detect it early is to obtain a urine sample and test for blood and/or protein.

Antibody tests and studies focusing on immune system abnormalities may add more insight into the patient's problems. The *rheumatoid factor* and *antinuclear antibody* are markers for RA and SLE or Sjögren's syndrome but may be elevated in certain forms of vasculitis or may indicate that the vasculitis is secondary to one of these illnesses. *Complement* is a protein in the bloodstream that is low when the immune system is activated in certain forms of vasculitis and can also serve as a clue to the diagnosis. *Cryoglobulins*, proteins that thicken the blood in cooler temperatures, can be measured in the lab and help identify patients with many types of vasculitis. Perhaps the most useful antibody marker is the *antineutrophil cytoplasmic antibody (ANCA)*. This antibody, discovered within the last few decades, is a much more specific marker for a number of different forms of vasculitis, particularly WG. Other conditions such as CSS and MPA also commonly exhibit a positive ANCA test. Moreover, the ANCA can also serve as a marker for disease activity in certain patients.

Other laboratory investigations may be in order to rule out secondary causes of vasculitis. Other than some of the antibody tests mentioned above, tests for exposure to hepatitis, HIV, and other infections is worthwhile, particularly in those at risk for these conditions. It is noteworthy that cryoglobulinemic vasculitis is associated with hepatitis C infection in the majority of cases, a finding that has a major impact on therapy.

In spite of all the above tools that can help identify vasculitis, the "gold standard" for a confident diagnosis is *biopsy* of the area where the disease is most active or in the area where such a procedure can most easily be carried out. This is most easily performed on the skin if abnormalities are present but can be performed on other organs with a fair degree of safety. In such instances where the kidneys, intestines, lungs, or other organs are being jeopardized, the risk of obtaining a biopsy from these areas is generally justified. This is most direct way of clearly documenting blood vessel inflammation, which can directly be observed under the microscope.

In situations where larger blood vessels are believed to be involved or where a biopsy would be hazardous, an *arteriogram*, or *angiogram*, is a reasonable alternative. This procedure involves injecting dye into the blood vessels of interest and observing the changes under an x-ray viewer. Smooth narrowing, dilation, or a "beaded" appearance of the vessels are all suggestive of vasculitis, but all of these findings still must be

distinguished from cholesterol plaques in the vessels, particularly in older patients. A *magnetic resonance imaging (MRI)* or *magnetic resonance angiogram (MRA)* may visualize changes suggestive of vasculitis, particularly in the brain, but while these studies are easier on the patient, they are not as accurate at defining abnormalities in blood vessels as the standard arteriogram.

Therapy: Appropriate treatment of vasculitis is as variable as the many illnesses included under the category of vasculitis. Because many of these illnesses are uncommon, extensive and well-designed studies are often difficult to find. The practitioner is left to use a combination of the best information available and his/her own experience and judgment in treating many of these illnesses.

In the case of vasculitis that is isolated to the skin, such as LCV, treatment is given based upon symptoms and severity of disease. In some patients, the vasculitis may resolve without therapy or may respond to discontinuation of a medication or other factors that may have triggered the illness. Most patients require some form of therapy, which may include *antihistamines*, *colchicine*, a medication also used to treat gout and other inflammatory diseases; *dapsone*, a medication used to treat leprosy and other skin diseases; or *hydroxychloroquine* (trade name *Plaquenil*), a medication also used to treat RA or SLE. Only in severe cases are *corticosteroids* required. These medications suppress inflammation quickly but long-term use is associated with weight gain, weakening of the bones, cataracts, elevation of blood sugar levels, and other side effects (see Medications section).

When the complications of vasculitis affect other organs, the situation changes. In these patients, aggressive therapy is in order. Most patients with these types of vasculitis warrant treatment with high-dose cortico-steroids as initial therapy. In patients with PAN, MPA, CSS, PACNS, TA, or GCA, steroids may be all that is necessary, and if an adequate response is seen the dose can be reduced and eventually discontinued. In patients with ongoing damage or more severe disease, *immunosuppressive drugs* such as *cyclophosphamide (CYC)*, *azathioprine (AZA)*, *methotrexate (MTX)*, or a newer medication known as *mycophenolate mofetil (MMF)*, trade name *Cellcept* have been used with success. Infection, lowering of blood counts, and liver damage are potential side effects of many of these medications that have to be carefully monitored.

A special situation exists in patients with WG. This condition, which was once almost universally fatal, can now be put into remission in up to 90% of patients by using a combination of steroids and oral CYC. Because side effects are a problem with the use of CYC long-term, many authorities are recommending converting to maintenance therapy with other drugs that can be used more safely long-term (MTX, AZA, or MMF) once the disease is under control.

Newer medications that have been used in other rheumatic diseases are under investigation for certain forms of vasculitis. These drugs, known as *biologic response modifiers*, must be given by vein or by injection. Examples include *tumor necrosis factor inhibitors*, a drug that block the effects of certain white blood cells known as *rituximab*, and a drug that also has activity against viruses such as hepatitis know as *interferon*.

Before better studies are available, all of these medications should be used only when standard treatment has failed or has been associated with intolerable side effects.

When another illness or exposure has triggered the vasculitis, treating the underlying condition is prudent. An example is hepatitis C-associated cryoglobulinemia, which is most appropriately treated by a combination of corticosteroids to reduce acute inflammation and antiviral therapy to rid the body of the infection. As mentioned above, when drug-induced vasculitis is suspected, the medication believed to be responsible can be withdrawn, but this should only be done under the supervision of the treating physician.

Many forms of vasculitis may require treatment for roughly 2 years (PAN, MPA, CSS, PACNS, or GCA, for example), after which time therapy can be slowly withdrawn. Other conditions (WG and TA) tend to require therapy for longer periods of time or may relapse when treatment is withdrawn. Careful supervision by the treating physician is needed to determine the ideal duration of therapy for each individual patient. The many forms of vasculitis are indeed challenging to diagnose and treat, but in the hands of an experienced and thorough physician optimal outcomes for such patients can be achieved.