CHAPTER

# 10

# *Vasculitis*

**V. Shantaram**

## Introduction

There is nothing more challenging to the primary care physician or Rheumatologist than a case of possible systemic vasculitis. A thorough history, physical examination and focus directed serological and radiographic studies are of extreme importance in making a diagnosis.

## Definition

Vasculitis is a heterogeneous group of disorders characterized by the pathological features of inflammation within the walls of affected blood vessels. The pathological consequence of such inflammation is often destruction of vessel wall seen on histology as fibrinoid necrosis hence the term "necrotizing vasculitis."

## Classification

The primary vasculitis is classified on the basis of size of the vessels involved into large vessel medium vessel or small vessel vasculitis.[1] Secondary vasculitis occurs associated with other known underlying conditions like infections, autoimmune diseases, inflammatory bowel disease, malignancies and as reaction to drugs.

## Physicians Clinical Approach

High index of clinical suspicion of vasculitis should be in the mind of practicing physician when he encounters a patient with unexplained ischemia or multiple organ involvement in the form of arthritis, palpable purpura, glomerlonephritis or multiple mononeuropathy. When systemic vasculitis is suspected the first step is to exclude other processes such as connective tissue disorders (RA, SLE, etc.), infection (Bact. Endocarditis, viral, fungal, etc.), malignancy, drug reactions (Table-3). If primary vasculitis is clinically diagnosed then try to classify the disorder on the basis of the size of the vessels involved into large medium or small vessel vasculitis (Table-1). After determining the size of major vessels involved other issues that contribute to the classification include:

- Does the process involve arteries, veins, or both?
- What are the patients demographic characteristics? (sex, age, ethnicity, smoking status)
- Which organs are involved.
- Is there evidence of immune complex deposition?
- Is there granulomatous inflammation on tissue biopsy?
- Are anti-neutrophil cytoplasmic antibodies present (ANCA).

**Table I : Classification scheme of vasculitis according to the size of predominant blood vessel involved**

| | |
|---|---|
| **Large Vessel Vasculitis :** | a. Takayasu's arteritis |
| | b. Giant Cell arteritis (Temporal arteritis) |
| | c. Behcet's disease |
| **Medium Vessel Vasculitis :** | a. Poly arteritis nodosa |
| | b. Buerger's disease. |
| **Small Vessel Vasculitis :** | |
| a. Immune Complex mediated | b. ANCA Associated disorders |
| • Cutaneous leukocytoclastic angiitis | • Wegner's granulomatosis |
| • Henoch Schonlein Purpura | • Microscopic polyangiitis |
| • Essential Cryoglobulinemia | • Churg-Strauss Syndrome. |

**Table 2 : Typical clinical manifestation of large, medium, and small vessel involvement by vasculitis**

| Large | Medium | Small Vessel |
|---|---|---|
| **Constitutional Symptoms : Fever, weight loss, malaise** | | |
| **Arthralgia or arthritis are common to all** | | |
| * Limb Claudication | * Cutaneous nodules | * Purpura |
| | * Ulcers | * Urticaria |
| * Asymmetric blood pressure | * Livedo reticularis | * Glomerulo Nephritis |
| * Absence of pulses | * Digital gangrene | * Alveolar Hemorrhage |
| * Bruits | * Mononeuritis multiplex | * Uveitis |
| * Aortic dilation | * Micro Aneurysms | * Episcleritis |
| | | * Cutaneous vasculitis |

**Table 3 : Conditions that mimic vasculitis**

| | |
|---|---|
| * Sepsis | * Sarcoidosis |
| * Endocarditis | * Lymphoma |
| * Granulomatous infection(T.B., Fungal) | * Hairy cell leukemia |
| * Hepatitis A B C, HIV, CMV infections | * Myelodysplasia |
| * Lyme disease | * Metastatic solid tumors |
| * Cholesterol Embolic Syndrome | * Thrombotic thrombocytopenic purpura |
| * Disseminated intravascular coagulation | * Coumadin skin necrosis |
| * Antiphospholipid antibody syndrome | * Vaso reactive drugs [cocaine, ergot, amphetamine] |

Though the classical clinical presentation may be encountered (Table-2), not uncommonly primary vasculitic syndromes overlap and do not fit neatly into a well defined type when the term "undifferentiated systemic vasculitis" may be used and close follow up of the patient may be required looking for the signs that lead to specific diagnosis.[2]

## Investigative Work Up

Laboratory investigation help the Physician to diagnose vasculitis and classify it besides helping him to determine various organ involvement. Anemia of chronic disease high Erythrocyte Sedimentation rate, elevated C-reactive protein are indicators of active disease. Renal failure in

**Table 4 : ANCA Immunofluorescence patterns[4]**

| Patterm | Description | Main disease association | Others |
|---|---|---|---|
| Typical C-ANCA | Cytoplasmic staining with interlobular accentuation | Wegner's granulomatosis Sens 80%, Spec 95% | MPO<br>CSS<br>PAN |
| Typical P-ANCA | Perinuclear staining with nuclear extension | Microscopic polyangiitis<br>Churg-Strauss Syndrome (Sen 60%, Specificity 75%) | WG<br>PAN |
| Atypical C-ANCA | Diffuse cytoplasmic pattern without interlobular accentuation | Malignancies<br>Drug induced vasculitis | |
| Atypical P-ANCA | Perinuclear pattern without nuclear extension | SLE and other rheumatic diseases, chronic infections | |

a patient with proteinuria and hematuria suggest glomerulonephritis. Chest radiograph may reveal asymptomatic pulmonary involvement. Nerve conduction studies and electromyography can help confirm clinical findings suggestive of neuropathy or muscle involvement.

## Anti-Neutrophil Cytoplasmic Antibodies (ANCA)[3]

ANCA Testing is a routine in a suspected cases of systemic necrotizing vasculitis, i.e., Wegner's Granulomatosis (WG) microscopic polyangiitis (MPA), Churg-Strauss Syndrome (CSS) and poly arteritis nodosa (PAN).

Antineutrophil cytoplasmic antibodies (ANCA) are a group of autoantibodies that bind to cytoplasmic granules present in neurophils. These are of two principal types.

1) **C-ANCA** : There are antibodies to proteinase-3
2) **P-ANCA :** There are antibodies to myeloperoxidase, lectoferrin and elastase the proinflammatory enzymes found in neutrophils. Release of these enzymes after exposure to ANCA result in local tissue necrosis.

**Atypical ANCA** are antibodies directed against lectoferrin cathepsin G, elastase, lysozyme and bacterial permeability increasing proteins. It shows high association with drug induced vasculitis.

**Hepatitis B & C** and HIV serologies should be obtained since these infections are sometimes associated with vasculitis.

**Complement levels** C3, C4, CH5O tend to be low in SLE associated vasculitis, cryoglobulinemia. They may be normal in other vasculitis.

**Cryoglobulins** can be present in malignancy (Lymphoma, leukemia, plasma cell dyscrasias) chronic infections (Hepatitis B & C and Endocarditis), mixed essential cryoglobulinemia a syndrome strongly associated with hepatitis C.

**Biopsy** open biopsy of symptomatic sites if feasible is preferred. The yield of blind biopsy from asymptomatic sites is low. In a patient with multi system illness and testicular pain, testicular biopsy should be considered. A temporal artery biopsy is indicated in an elderly with a new unexplained headache and raised ESR. Sural nerve biopsy is useful in a patient with peripheral neuropathy.

**Angiography** is useful to provide definite diagnosis in cases of extremity ischemia, claudication or suspected mesenteric or renal vasculitis. MR angiography may confirm Takayasu's vasculitis.

**Computed Tomography** of Chest may be helpful in differential diagnosis of vasculitis with pulmonary involvement differentiating fixed cavitary nodules of Wegner's granulomatosis from

migratory non-cavitating nodules of Churg-Strauss Syndrome.

## Overview of Primary Vasculitic Syndromes

**Large Vessel Vasculitis** – include Giant cell arteritis and Takayasu's arteritis.

1. *Giant Cell Arteritis (GCA) :* is a granulomatous vasculitis of the aorta and its major branches in patients over the age of 50 years. The condition is also called temporal arteritis as that vessel is frequently involved. The classic symptoms consist of headache, scalp tenderness, visual symptoms, jaw claudication or throat pain. The temporal artery may be normal or maybe nodular, enlarged, tender or pulse less. Blindness usually results from anterior ischemic optic neuropathy. The fundus initially may be normal despite sudden blindness. In 25% aorta and its major branches may be affected with aneurysm of thoracic aorta or stenosis of subclavian artery resulting in asymmetry of pulses in arms, bruit near clavicle. In elderly it may present as Fever of Unknown Origin with raised ESR in 15% of patients usually the total leukocytic count in normal. Respiratory system is involved in 9-31% dry cough with fever being the common presentation. Less commonly sore throat, chest pain occurs; pleural effusion and Interstitial Lung Disease rarely occurs. The diagnosis of Giant Cell Arteritis is confirmed by temporal artery biopsy preferably under sonographic guidance which highlights potential areas of involvement. Treatment is with high dose corticosteroids 40 – 60 mg of Prednisone started as soon as the diagnosis is suspected to avoid visual loss. The steroids may be tapered by 10 mg per week over six months with maintenance of 5 – 10 mg/daily for two years. The disease activity is commonly evaluated by the ESR, CRP and recently IL-6 is proved to be a useful indicator though not routinely done. Low dose aspirin 81 mg may be useful along with steroids.
2. *Polymyalgia Rheumatica* is a clinical diagnosis based on pain and stiffness of the shoulder and pelvic girdle areas frequently in association with fever, malaise and weight loss. A few patients have joint swelling particularly of the knees, wrists and sternoclavicular joints. Anemia and markedly elevated ESR are almost always present. Steroid therapy with 10-20 mg Prednisone produces dramatic improvement within 72 hours and if it does not occur diagnosis should be revised.
3. *Takayasu's Arteritis* is commonly seen in young females in Asian and far East countries. Symptoms include malaise, arthralgia and extremity claudication. The aorta and its proximal branches are involved though thoracic and abdominal aorta, pulmonary arteries and coronary arteries are also involved.[5] Diagnosis is made by angiography or MR angiography. In acute phase steroids are useful. Cytotoxic drugs like cyclophosphamide or methotrexate may be added. Surgery or angioplasty may be required for stenosis once inflammation is controlled.

## Medium Vessel vasculitis

1. *Polyarteritis Nodosa :* This disorder is characterized by necrotizing arteritis of medium sized vessels that has a predilection for involving peripheral nerves, mesenteric arteries, renal arteries, cerebral and coronary vessels. About 10% of polyarteritis nodosa are caused by hepatitis B.[6] The clinical features include fever, other constitutional symptoms, abdominal pain, livedo reticularis, mononeuritic multiplex, anemia and raised ESR are common. Hypertension is common. Lungs are spared. The diagnosis is based on clinical suspicion while angiography reveals arterial, aneurysms of the renal, splanchnic, hepatic or splenic vessels. Biopsy of the affected nerve or muscle sometimes testicular biopsy if pain exists will confirm the disease. Treatment consists of high dose steroid therapy with 60 mg of Prednisone

initially followed by gradual tapering of the dose is advised. In critical sitting pulse Methyl Prednisolone 1 G I.V. for 3 days may be helpful. Cyclophosphamide is recommended additionally in severe cases for better results and survival. In Hepatitis B positive patients anti viral drugs like Lamivudine 100 mg/daily and Plasmapheresis three times a week for upto 6 weeks may be tried. Interferon alfa along with steroids is also useful.

2. *Kawasaki Disease* affects infants and small children. In Japan the incidence exceeds 100/100000 children younger than 5 years.[7] The large, medium and small arteries may be affected in association with mucocutaneous lymph node syndrome. The most serious feature is coronary artery disease with occurrence of aneurysms and myocardial ischemia. High dose of immunoglobulin is advised especially useful, if given within 10 days of the diagnosis.

## Small Vessel Vasculitis Associated with A.N.C.A.

This group consists of heterogenous disorders carrying unfavorable prognosis if not diagnosed early. The early symptoms are nonspecific with fever, malaise, arthralgia, myalgia and weight loss. The patients should be screened for ANCA. Early diagnosis is essential to prevent fatal renal and pulmonary injury.

### Wegner's Granulomatosis (WG)

WG is a systemic granulomatous inflammatory process involving small vessels with variable clinical expression. It classically involves upper and lower respiratory tracts and kidneys. Limited WG refers to disease that affects only the respiratory tract at the time of diagnosis. The condition typically manifests by recurrent sinusitis epistaxis, mucosal ulceration and otitis media. Destructive charges may lead to saddle nose or tracheal stenosis. Lung disease presents with cough, hemoptysis, dyspnea and progress to pulmonary hemorrhage. The granulomas in the lung may coalesce and then cavitate. The kidney is involved in upto 80% of patients in the form of either segmental, focal or diffuse glomerulonephritis. The renal injury with failure occurs within days, if untreated.

**Microscopic Polyangiitis** is a variant of polyarteritis nodosa commonly presents as pulmonary hemorrhage and glomerulonephritis. Clinically cough, dysphasia, hemoptysis, myalgia and arthralgia occur. Chest radiograph reveals bilateral areas of consolidation due to diffuse pulmonary hemorrhage. Pathologically there is panmural infiltration with destruction of vessel wall by neutrophils with fibrinoid necrosis.

**Churg-Strauss Syndrome** occurs in the setting of atopic tendency usually asthma, allergic rhinitis and eosinophilia. It may affect coronary, pulmonary, cerebral, splanchnic and subcutaneous nodules are common. Pulmonary transient and patchy alveolar infiltrates without lobar or segmented distribution represent the most frequent radiological findings. Diagnosis depends on typical clinical features with biopsy of skin, lung, kidneys confirming vasculitis besides eosinophilic leukocytosis and positive P-ANCA in 50% C-ANCA 25%.

## Treatment of ANCA Associated Small Vessel Vasculitis

Oral cyclophosphamide (2 mg/kg/day) and prednisolone 60 mg is initially given and gradually tapered over 12 weeks.[8] The cyclophosphamide should be discontinued if total leukocyte count falls to 4000/c.mm. If no significant renal disease is present methotrexate 20 – 25 mg/week is advised as a substitute to cyclophosphamide. Azathioprine 2 mg/kg may be also used as a substitute to cyclophosphamide after 3 months of initial therapy for maintenance purpose for 1 – 1½ years.

## Small Vessel Vasculitis without ANCA

1. **Henoch Schonlein Purpura** is most commonly seen in children. Typical features include purpura over limbs, hematuria, abdominal pain, bloody diarrhea and arthritis. The hall mark is deposition of IgA at the dermo epidermal

function and in glomerular mesangium. The disease is self limiting. Steroids are advised if serious renal or gut lesion occur.

2. **Isolated Cutaneous Leukocytoclastic Vasculitis** : This disorder frequently presents as palpable purpura though urticarial and ulcerative lesions may occur. Drug reaction, infection, neoplasms and primary connective tissue diseases may present with this clinical picture. Steroid therapy may be required.
3. **Cryoglobulinemic Vasculitis** : Cryoglobulins are immune globulins that precipitate with cold. The mixed cryoglobulins consists of monoclonal IgM rheumatoid factor complex to polyclonal IgG. Vasculitis develops when cryoglobulin deposit in blood vessels. Mixed essential cryoglobulinemia is due to hepatitis C virus infection (in 80%), clinically palpable purpura, arthralgia, digital gangrene, peripheral neuropathy, abdominal pain and glomerulonephritis are encountered. In Hepatitis-C associated disease interferon alfa with or without ribavirin is beneficial. In acute severe cases corticosteroids with other immuno-suppressive therapy is recommended.

## Conclusion

Systemic Vasculitis is a Physicians challenge and encompasses a heterogenous group of disease. Early diagnosis and treatment are important to avoid significant mortality and morbidity. Much progress has been made in the diagnosis and treatment. Long term survival is now possible for previously fatal form of disease. Current research has focused on the use of alternative form of immuno-suppressive therapy. Major advances will require a better understanding of pathogenesis of these fascinating disorders.

## References


1. Jennette J.C. Falk RJ, Androssy K, et al. Nomenclature of Systemic Vasculitides. Proposal of an International Consensus Conference. Arthritis Rheum. 1994: 37, 189-92.
2. Roane P.W. Griger DR. An approach to diagnosis and management of Systemic Vasculitis. Am Acad Fan Physician, 1999; 60: 1421-30.
3. Rao JK, Weinberger M, Oddone E, et al. The role of antineutrophilic cytoplasmic antibody C-ANCA testing in the diagnosis of Wegner's granulomatosis. Ann Intern Med 1995; 21: 883-909.
4. V.R. Joshi, Aparna Rao. Approach to ANCA Medicine Update. API, Vol 17, editor R.K. Singal, 2007; Chapter 146, 844-850.
5. Mantosh Panja, Prakash Chandra Mondol. Takayasu Disease: A Pan arteritis, Postgraduate Medicine, API, Vol 18, 2004, editor Lekha Adik Pathak, Chapter 24; 191-196.
6. Lhote F. Guillevin L. Polyarteritis nodosa Microscopic polyangiitis, Churg-Strauss Syndrome Clinical aspects and treatment. Rheum Dis Clin North Am 1995, 21: 911-47.
7. Petty RE, Cassidy JT, Kawaseki disease. Text book of Pediatric Rheumatology, 4$^{th}$ed Philadelphia, Saunders 2001, 580-93.
8. Savage CO, Harper L, Cockwel P, Adu D, Howie AJ. Vasculitis. BMJ 2000, 320: 1325-287.
9. Jayne D. Rasmussen N, Androssy K, et al. A Randomised trial of maintenance therapy of vasculitis associated with antineutrophil cytoplasmic auto antibodies. NEJM 2003, 349; 36-44.