Small Vessel Vasculitis And the Pulmonary-Renal Syndrome

Christine D’Arsigny, MDCM, FRCP, FCCP, Associate Professor, Department of Medicine, Division of Respirology and Critical Care Medicine, Kingston General Hospital, Queen’s University

Small vessel vasculitis

In all of these conditions, there is inflammation of small to medium sized vessels such as capillaries, venules, arterioles and arteries. Granulomas are found in Wegener’s granulomatosis and Churg-Strauss syndrome, but not the others and there is a strong correlation with anti-neutrophil cytoplasmic antibodies (ANCA) in Wegener’s granulomatosis, Churg-Strauss syndrome and microscopic polyangiitis.

Medium vessel vasculitis

Polyarteritis nodosa (PAN): necrotizing inflammation of medium or small arteries. Unlike microscopic polyangiitis, there is NO glomerulonephritis and NO vasculitis in arterioles, capillaries, or venules

Kawasaki disease: arteritis of large, medium and small arteries, usually in children. Often involves the coronary arteries and can be a cause of significant morbidity

**Medium sized vessels refer to the main visceral arteries such as renal, hepatic, coronary and mesenteric**

Large vessel vasculitis

Giant cell (temporal) arteritis: arteritis of the aorta and its major branches, especially the extracranial branches of the carotid artery; associated with polymyalgia rheumatica.

Takayasu arteritis: arteritis the aorta and its major branches

In these conditions, granulomatous arteritis is the histopathologic finding to as the pulmonary-renal syndrome. The first 3 listed diseases are associated with anti-neutrophil cytoplasmic antibodies (ANCA), and this review will focus on the diagnosis and treatment of these three vasculitides.

Continued on page 4
EDITORIAL

Simon Carette, MD, MPhil, FRCP, Professor of Medicine, Director, University of Toronto Vasculitis Clinic, Head, Division of Rheumatology, University Health Network/ Mount Sinai Hospital

A NCA-related vasculitides (AAV), including Wegener’s granulomatosis (WG) and microscopic polyangiitis (MPA) account for 60% to 70% of patients presenting with the combination of pulmonary hemorrhage and glomerulonephritis (1). Although few in number, outcome studies of pulmonary renal syndrome report an early mortality rate of up to 50% with cyclophosphamide-induced neutropenia and infection being frequent contributors to death (1,2).

In this issue of the Ontario Thoracic Review, Dr. D’Arsigny presents an approach to the diagnosis and management of pulmonary renal syndrome associated with AAV. An issue often raised in relation to the investigation of these patients is whether a positive ANCA can replace histology. Given the very high positive predictive value for a diagnosis of AAV in this clinical setting when ANCA are positive by both indirect immunofluorescence and ELISA techniques (> 98%), I believe that biopsies can be deferred and even eliminated altogether particularly in very sick patients in whom they cannot be performed safely.

All authors agree with corticosteroids and cyclophosphamide currently being the treatment of choice in patients with pulmonary renal syndrome secondary to AAV. In order to minimize the risk of neutropenia and infection, it is recommended to reduce the dosage of cyclophosphamide by half in patients with a creatinine clearance of less than 10 ml/min. Plasma exchanges (PE) should also be considered in patients with renal failure requiring dialysis. This recommendation is supported by the results of the MEPEX trial in which 151 patients with acute renal failure secondary to AAV (creatinine > 500 mmol/l) were randomized to receive either 7 PE (each of 60 ml/kg) within 2 weeks, or three pulses of IV methylprednisolone MPP (15 mg/kg), in addition to oral cyclophosphamide and prednisolone. Sixty-eight percent of the patients who received PE were alive and off-dialysis at 3 months as compared to 48% of those who received the MPP pulses (3). Whether PE should also be given to patients with pulmonary hemorrhage and to those with less severe renal involvement is presently unclear.

The rate of disease relapse is very high in patients with WG (50-60%) and MPA (30%) particularly in the year following the discontinuation of immunosuppressive therapy. Because of this, immunosuppressive medications (azathioprine, methotrexate or mycophenolate mofetil) should be continued for a minimum of 24 months after the induction of remission and sometimes even longer particularly in patients in whom ANCA remain positive. Data from the CYCARAZEM trial suggest that patients should also remain on low dose prednisone (7.5 mg/day) for a minimum of 18 months following remission (4).

Recent data from animal models confirmed that AANCA play a direct role in the pathogenesis of AAV (5). In that context, the elimination of CD20-positive B lymphocytes by rituximab may represent a very promising and potentially safer approach to AAV than current therapies. It is hypothesized that B cells returning after treatment (6-12 months) will be tolerant to PR3 and MPO, thus providing long-term and perhaps even permanent clinical remission. A multicentre randomized clinical trial sponsored by the NIH is currently underway in the US and Canada to test this hypothesis.

REFERENCES


RESPIROLOGY JOB FAIR AT BETTER BREATHING 2007

Please plan to attend the 4th annual Respirology Job Fair to be held on Friday, February 2, 2007 at 5:00 p.m. at Better Breathing 2007. You will have an opportunity to present information about positions available in your centre (academic or community) to all residents in the Respirology and combined Respirology/Critical Care Programs in Ontario. The Respirology Program Directors will be present if you wish to discuss the future needs of your centre. Informal mingling allows for plenty of opportunity to meet the upcoming graduates of the Ontario Respirology Programs.

Hope to see you there!
Antineutrophil cytoplasmic antibodies

ANCA are specific antibodies that are directed at antigens within the cytoplasmic granules of neutrophils and monocyte lysosomes, and are associated with the small vessel vasculitides. ANCA was originally detected by immunofluorescent techniques, with c-ANCA (cytoplasmic) directed against proteinase-3 (Figure 1) and p-ANCA (perinuclear) directed against myeloperoxidase (figure 2). Proteinase-3 and myeloperoxidase usually reside in the azurophil granules of the neutrophil and are normally involved in host defense against invading organisms23. In addition to proteinase-3 and myeloperoxidase, ANCA can target other proteinases found within the neutrophil granules such as elastase, cathepsin G, lactoferrin, lysozyme, b-glucuronidase; and in the neutrophil cytoplasm such as c-enolase, ANCA can also target infection-related antigens such as bacterial permeability increasing protein (BPI), human lysosome associated membrane protein 2 (H-lamp-2), defensin, and azurocidin, which suggests that ANCA may be associated with various infections. It is already known that ANCA may be positive in subacute bacterial endocarditis and patients with cystic fibrosis. There is also evidence that intercurrent infection can lead to an exacerbation in patients with systemic vasculitis and that nasal carriage of Staphylococcus aureus predisposes to relapse in patients with systemic vasculitis23. Unfortunately, different laboratory methodologies in immunofluorescence can lead to very different results in terms of presence and quantity of ANCA. Thus, immunofluorescence alone is not helpful in the diagnosis of small vessel vasculitis.

An enzyme-linked immunosorbent assay (ELISA) method has since been standardized and uses purified native proteinase-3 (PR3) and myeloperoxidase (MPO), directly coated on microwells. Due to the high sensitivity and specificity of the ELISA test, is useful in the diagnosis of small vessel vasculitis and excluding systemic inflammatory diseases24. The European study on standardized ANCA assays found that ANCAs should only be reported positive if both the immunofluorescent and ELISA test for either PR3-ANCA or MPO-ANCA are clearly positive25. A positive ANCA could then be attributed to be due to a small vessel vasculitis. This would then exclude systemic inflammatory diseases that cause minimal production of PR3-ANCA or MPO-ANCA, but have a positive immunofluorescent test. Some of these disorders include spontaneous bacterial endocarditis, active tuberculosis, cystic fibrosis, systemic lupus erythematosus, rheumatoid arthritis, and HIV infection.

Clinical Manifestation of small vessel vasculitis

Small blood vessels of any organ can be affected resulting in a wide variety of signs and symptoms. Common clinical manifestations for the ANCA positive small vessel vasculitides include renal failure from glomerulonephritis, pulmonary hemorrhage and/or pulmonary infiltrates, and constitutional symptoms such as flu-like symptoms, arthralgias, myalgias and fever.

In Churg Strauss syndrome, patients may have symptoms of asthma, neurologic findings, abdominal pain and/or cutaneous lesions. In order to make the diagnosis, the patient must have 4 of the following diagnostic criteria: (1)asthma, (2) >10% eosinophilia, (3)mono- or polyneuropathy, (4) fleeting pulmonary infiltrates, (5) paranasal sinus abnormality and (6) extravascular eosinophils26. The mean age of onset for this form of vasculitis is 45 years, with a 2.5:1 male-to-female ratio. The annual incidence is between 3.3-4.0 cases/million population. Thirty percent of patients are found to be Hepatitis B surface antigen positive and 70% will have a positive ANCA level. The natural history of Churg Strauss syndrome is variable, with the disease ranging from relatively indolent to rapidly fatal vasculitis.

Wegener’s Granulomatosis requires at least 2 of the 4 diagnostic criteria to make the diagnosis: (1) nasal or oral inflammation, (2) abnormal chest radiograph (nodules, infiltrates or cavities), (3) red cell casts or microhematuria, (4) granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area on biopsy27. Symptoms can be variable, but nasal, sinus, tracheal or ear abnormalities are present initially in 73% and eventually in 90%. Two thirds of patients will have cough, pleuritis or hemoptysis with 85% having some respiratory complaint during the disease progression. Seventy five percent develop overt glomerulonephritis within 2 years of disease manifestation, yet 18% have asymptomatic glomerulonephritis at presentation. Renal disease is a marker of poor prognosis. Other symptoms can develop from the ocular, cardiac, gastrointestinal tract, musculoskeletal system, skin or central nervous system. The mean age of onset is 50 years of age and there is no gender predilection. The annual incidence for this disorder is 20 cases/million population.

Microscopic polyangiitis involves any organ including the respiratory tract where it can present with fleeting infiltrates, hemoptysis and massive pulmonary hemorrhage. Glomerulonephritis develops in 90% of patients and skin lesions are most commonly due to leukocytoclastic angiitis. Mononeuritis multiplex is the most common neurologic manifestation and abdominal pain in often caused by bowel ischemia.
Small Vessel Vasculitis And The Pulmonary-Renal Syndrome...

Granular deposits of immunoglobulin and complement are found in vessel walls and glomeruli in the non-ANCA positive small vessel vasculitides (IgA-dominant deposits in patients with Henoch Schonlein purpura; deposits of IgG-IgM in patients with mixed cryoglobulinemia, and IgG-dominant deposits in lupus vasculitis and septic vasculitis). Few, if any, immune deposits (pauci-immune) occur in target tissue in Wegener’s granulomatosis, Churg Strauss syndrome and microscopic polyangiitis. Goodpasture’s syndrome, which can present with pulmonary renal syndrome is ANCA negative and has linear staining of alveolar and glomerular basement membranes (GBM) due to anti-GBM antibodies that cross react with alveolar basement membrane.

Diagnosis

The evaluation of a patient with possible small vessel vasculitis requires a consistent history and physical exam, serologic tests, urine microscopy and analysis, radiography +/- biopsy. Serologic tests include complete blood count with differential, renal function, erythrocyte sedimentation rate, complement levels, anti-glomerular basement membrane antibody tests for Goodpasture’s disease, antinuclear antibodies for lupus, anti-streptococcal antibodies for post streptococcal glomerulonephritis (antistreptolysin O titer increased in only 50%; anti-DNAase B or hyaluronidase are often required to diagnose recent streptococcus infection), blood cultures for bacterial endocarditis, and ANCA for Wegener’s granulomatosis, Churg-Strauss syndrome and microscopic polyangiitis.

ANCA sensitivity depends on disease activity and extent. C-ANCA is positive in over 90% with active Wegener’s granulomatosis. In limited Wegener’s granulomatosis (without the active glomerulonephritis) or in inactive disease, the sensitivity of c-ANCA may be as low as 43% or as high as 65-70%. P-ANCA may be positive in 5% with Wegener’s granulomatosis, but is usually associated with other vasculitic syndromes (Table 3) such as Churg-Strauss syndrome and microscopic polyangiitis.

All patients should have a chest radiograph, with consideration made to ordering a CT of the chest to help identify small nodules and localize region of air space involvement. Biopsies are obtained from the involved organ and urine is evaluated for evidence of hematuria, proteinuria and cast formation.

Table 4 summarizes an approach to the diagnosis of small vessel vasculitis.

Treatment

Treatment includes 3 phases: the induction of remission, maintenance of remission and treatment of relapse. The treatment of Churg Strauss syndrome usually responds to high dose steroids alone. Less than 20% will need immunosuppressants, usually for major life-threatening organ involvement as occurs with cardiac, renal or neurologic involvement. The typical prednisone dose is 0.5-1mg/kg/day or 40-60 mg orally with a taper occurring over 6 to 12 weeks as symptoms resolve. If cyclophosphamide is used, it is typically given at doses of 1-2mg/kg/day orally or pulsed every month at doses of 500-1000mg/m² IV. Monitoring response to treatment is best achieved through the patient’s eosinophil count and erythrocyte sedimentation rate. A persistently positive ANCA level does not adequately reflect disease activity and should not be used in isolation to make changes in therapy. Few patients will relapse after successful response to therapy and treatment can be stopped in most patients. Other treatment options that have been proven to be of benefit in fulminant or refractory disease include intravenous immunoglobulin (IVIG), azathioprine and plasmapheresis.

The treatment for Wegener’s granulomatosis and microscopic polyangiitis, includes cyclophosphamide and steroids as part of induction therapy. Oral cyclophosphamide at 1.5-2 mg/kg/day is given to keep the white blood cell count above 4000/mm³ and

### TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>Wegener’s Granulomatosis%</th>
<th>Microscopic polyangiitis%</th>
<th>Churg-Strauss Syndrome%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-PR3 (c-ANCA)</td>
<td>65-75</td>
<td>35-45%</td>
<td>10%</td>
</tr>
<tr>
<td>anti-MPO (p-ANCA)</td>
<td>15-25%</td>
<td>45-55%</td>
<td>60%</td>
</tr>
<tr>
<td>negative</td>
<td>10-20%</td>
<td>10-20%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Ontario Thoracic Reviews Fall 2006

Continued from page 4
Small Vessel Vasculitis And the Pulmonary-Renal Syndrome...

TABLE 4

| Symptoms of vasculitis | ANCA Positive: Wegener's Granulomatosis, Microscopic angiitis, Churg Strauss syndrome | Granulomas on biopsy: Wegener's Granulomatosis, Churg Strauss syndrome | Asthma and eosinophilia: Churg Strauss syndrome | No granulomas on biopsy: Microscopic angiitis | No asthma and no eosinophilia: Wegener's granulomatosis |

is continued for 1 year after disease remission for a total duration of treatment of 18 months. Prednisone is usually started at doses of 1 mg/kg/day (maximum of 60-80 mg/day), or its equivalent. The dose should be maintained for at least 1 month. If significant improvements in symptoms occur, the prednisone dose is slowly tapered to reach 20 mg/day by the end of 2 months and 10 mg/day by 6 months and kept at 7.5 mg/day for the total duration of therapy (usually 18 months).

Other treatment options include pulse cyclophosphamide, which is usually given monthly at doses of 0.5-1.0 g/m² body surface area (dose adjustments needed for age and renal function). It appears to be as efficacious as oral daily dosing, although 1 study showed an increased relapse rate in patients receiving pulse therapy. However, other studies have shown a safer adverse event profile in the one monthly-dosing regimen. Pulsed methylprednisolone at doses of 250-1000 mg per day IV is often reserved for patients with fulminant respiratory or renal failure at presentation. After the first 3 days of treatment, oral prednisone is continued at 1 mg/kg/day.

In order to limit the side effects of cyclophosphamide, The CYCAZAREM study showed that there was no difference in relapse rates when cyclophosphamide was switched to azathioprine after induction of remission (after 3-6 months). There was also a trend for less serious adverse events in the azathioprine group. Other treatments have included cyclosporine with variable results, as well as mycophenolate mofetil and Methotrexate. The use of IVIG at 2 g/kg every 3 months as needed has been shown to be beneficial in the treatment of ANCA-positive vasculitis, with 45-75% response rate in small prospective trials. Potential modes of action may be due to the fact that it contains antibodies that may inhibit ANCA, has regulatory effects on both B- and T-cell levels and interacts with inflammatory factors such as complement and cytokines. However, adverse effects are frequent and include renal failure, vasculitis and inflammatory manifestations. Plasmapheresis has not been found to be of benefit with the exception of patients who present with severe renal disease (creatinine >504 mmol/L). Empiric use of plasmapheresis has also been used in patients with Wegener's granulomatosis who have concurrent anti-GBM antibody disease and patients with severe pulmonary hemorrhage.

Prophylactic drug therapy is also important in the treatment of small vessel vasculitis and includes trimethoprim-sulfamethoxazole to prevent pneumocystis carinii infection, proton pump inhibitors to prevent gastrointestinal erosion, antifungal suspensions and lozenges to prevent fungal infection, and bisphosphonates to prevent bone loss.

Relapse

Relapses occur in 30-50% of patients within the first year after stopping treatment, with the CYCAZAREM study reporting a relapse rate of 13.7%-15.5% using their protocol. Although recurrences often develop in the organ of initial involvement, this is not always the case and close follow up is required to identify early relapse. Treatment of relapse is similar to initial treatment, with consideration of the newer agents if the patients become refractory to treatment. Vasculitis may develop as a consequence of infection, such as in endocarditis, and relapse may be brought on by intercurrent infection. It is known that Staphylococcus aureus colonization of the upper respiratory tract increases the relapse rate in Wegener's granulomatosis whereas prophylactic treatment with trimethoprim-sulfamethoxazole decreases the relapse rate. PR3-ANCA patients are at a higher risk of relapse than those positive for MPO-ANCA, as are patients who have predominantly lung involvement compared to renal involvement. There is also a higher rate of relapse in patients whose ANCA levels rise after treatment has been discontinued. However, the frequency and time to clinical relapse once ANCA levels rise is unknown and patients are generally followed more closely to identify clinical relapse.

Toxicity

The CYCAZAREM trial found 1.1 adverse effects per patient with 26% having severe or life-threatening adverse effects within 18 months of treatment. Infectious complications were the most frequent cause of morbidity and mortality, with frequency associated with age and steroid dosage. Cyclophosphamide metabolites are known to cause cystitis and bladder cancer. The frequency of hematuria is related to duration and total dose of cyclophosphamide with 50% occurring after 40 months or 120 grams. Patients are unlikely to develop bladder cancer without the development of hematuria first, although in those with hematuria, the risk of malignancy is 5% at 10 years and 16% at 15 years. Gonadal failure is related to total cyclophosphamide dose and is likely more common in oral daily dosing regimens. Data from women with lupus nephritis show risk related to age and duration of therapy, with a 60% risk of infertility if the woman was >30 years of age.

Steroid induced bone disease is common due to the high cumulative exposure and age of the patient population. Cardiovascular disease is also increased, independent from the added increased risk of hyperglycemia and hypertension.

Outcome

Systemic vasculitis is usually fatal if left untreated and carries a worse prognosis in the elderly and in patients with renal failure. Patients with Churg Strauss syndrome do relatively well with treatment with rare disease-associated mortality. Initial reports of survival in Wegener’s granulomatosis was only 80% by the first year, however, with treatment, recent studies have reported only a 10% 1-year mortality and 24% 5-year mortality. The major cause of morbidity and mortality is complications from underlying organ dysfunction, such as renal failure, respiratory failure and less commonly cardiac ischemia or heart failure. As much as 25% of deaths have been attributable to opportunistic infections as a consequence of the immunosuppressant...
We are pleased to announce the first recipient of the “Breathe New Life Award” is David Hwang, MD, PhD. Dr. Hwang’s research project is entitled, “Role of the Pulmonary Microflora in Human Lung Transplantation”.

Dr. David Hwang is a pathologist and new investigator based at the Toronto General Hospital/University Health Network. A graduate of the MD-PhD program at the University of Toronto, he completed residency training in Anatomical Pathology at the University of Toronto, during which he co-authored a seminal paper on the pulmonary pathology of SARS. He was subsequently appointed as a pathologist specializing in thoracic pathology at the University Health Network and as an assistant professor in the Department of Laboratory Medicine and Pathobiology. His current interests are in the application of genomic and metagenomic strategies to investigate questions related to pulmonary infections and lung transplantation.

We would like to thank the OTS members for their donations through the Top It Up! for Respiratory Research Fund and the OLA for contributing the additional funds to make this first award possible.

Small Vessel Vasculitis And the Pulmonary-Renal Syndrome...

Conclusion

Patients suspected of vasculitis should have ANCA levels drawn to help confirm small vessel vasculitis. Urine microscopy, analysis and serum creatinine should be ordered looking for eosinophilia and vessel vasculitis. Urine microscopy, analysis and serum creatinine should be ordered to identify granulomatous lesions in Wegener’s granulomatosis and renal involvement. When possible, biopsy should be obtained to identify relapse and development of organ dysfunction.

REFERENCES


ONTARIO THORACIC REVIEWS Fall 2006