Cavitating pulmonary lesions and hemoptysis in a case of Wegener’s granulomatosis

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Case

A 49-year old gentleman was admitted for investigation of multiple cavitating pulmonary lesions on CT and hemoptysis (Figure 1). He developed a dry, non-productive cough a month prior to admission with fevers, chills, and night sweats, but no shortness of breath and no chest pain. Half a month prior to admission, he was diagnosed with pneumonia by chest X-ray and prescribed azithromycin. Without symptomatic relief after one week on antibiotics, his treatment regimen was changed to gatifloxacin and metronidazole for ten days. Three days later, the patient’s symptoms worsened to include a productive cough yielding yellow sputum, hemoptysis, muscle aches, epistaxis, and hematuria. He had also lost ten pounds the preceding month. The patient was deteriorating which prompted CT investigation showing multiple cavitation lesions.

The patient had quit smoking three years ago after a 30 pack-year history. He had an unremarkable medical history, and no family history of lung disease or vasculitis. He had no known previous exposures to farming, mining, or tending to birds. He had no significant travel history or exposure to tuberculosis.

On examination, the patient had a temperature of 38.9°C, a heart rate of 110 beats/min, blood pressure 127/72, and a respiratory rate of 16/minute, saturating 92-94% oxygen on room air. Examinations of cardiovascular and pulmonary systems were unremarkable. No finger clubbing was present. His hemoglobin was low at 89 g/L and creatinine high at 132 µmol/L. Urinalysis was positive for blood and protein, but negative for casts. Bacterial and fungal cultures were requested, as well as an initial vasculitis screen with serum ANA, rheumatoid factor, C-ANCA, P-ANCA, C3, C4, CH50, ESR, and CRP. The C-ANCA titre (Proteinase 3, PR3) was positive at 154 (> 30), strongly suggesting a diagnosis of Wegener’s granulomatosis (WG). He was
started on pulse prednisone and oral cyclophosphamide.

While in hospital, his renal function declined, with his creatinine rising to over 600 µmol/L. A trial of plasma exchange was initiated with five treatments over ten days. Renal function improved and he was fortunate to avoid hemodialysis. Hemothysis and hematuria improved with time. No renal biopsy was performed. He was started on oral Septra as prophylaxis against Pneumocystis carinii pneumonia and also given a no-salt-added diet. He was discharged 1 month after admission after he became stable. At discharge, his hemoglobin was low at 93 g/L and creatinine high at 407 µmol/L. He was to be reassessed and advised not to return to work.

Discussion

WG is a systemic vasculitis that is characterized by granulomatous lesions in the upper and lower respiratory tracts and focal necrotizing glomerulonephritis. All of the body’s small and medium-sized vessels can be affected resulting in many potential clinical manifestations (Table 1)\(^2\). These manifestations may suggest several vasculitic etiologies and diagnosis may prove to be a challenge. In this case, a common presentation of WG is discussed, where a supposed pneumonia, as shown on chest X-ray, does not resolve after treatment with multiple antibiotics. Combined with further symptoms and/or investigations, the circumstances point toward an alternate diagnosis (Table 2)\(^3\).

<table>
<thead>
<tr>
<th>Systemic</th>
<th>Fever, lethargy, weakness, weight loss, night sweats, skin lesions (rash and skin sores), arthralgias</th>
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</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>Pulmonary infiltrates, pulmonary nodules, hemothysis, pleuritis</td>
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<td>Kidney</td>
<td>Glomerulonephritis, hematuria, proteinuria</td>
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<tr>
<td>Ear, Nose, Throat</td>
<td>Sinusitis, nasal membrane ulceration and crusting, saddle nose deformity, epistaxis, hearing loss, ear pain, oral lesions</td>
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<tr>
<td>Eyes</td>
<td>Conjunctivitis, eye pain, visual loss</td>
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<tr>
<td>Nervous System</td>
<td>Peripheral neuropathy</td>
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The serum auto-immune anti-nuclear cytoplasmic antibody (ANCA) level is useful in both diagnosis and understanding the pathophysiology of WG. Patients with active WG are seen to have an auto-immune, antigen-dependent, inflammatory background, which is corroborated by CD4+ T cell and monocyte activation in active disease. Next, neutrophils are activated through the production of C-ANCA or P-ANCA by B-cells targeting either Proteinase 3 (PR3) or Myeloperoxidase (MPO), respectively\(^4\). However, the ANCAs are present in 85% of cases of active WG and are not pathognomic for the disease. Other ANCA-positive vasculitides are microscopic polyangiitis (MPA, 70% positive) and Churg-Strauss syndrome (50% positive)\(^4\). WG is mostly C-ANCA positive while MPA...
is mostly P-ANCA positive, but this differentiation is not clinically significant as treatment for both conditions is similar. Churg-Strauss presents a different clinical picture and generally includes asthma in 95% of patients, among other atopic allergic symptoms.

Table 2. Typical Differential Diagnosis for Hemoptysis with Cavitating Lung Lesions

<table>
<thead>
<tr>
<th>Neoplasms</th>
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<tr>
<td>Infectious</td>
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<td>Tuberculosis</td>
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<tr>
<td>Histoplasmosis, Aspergillosis, or Coccidiomycosis</td>
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<tr>
<td>Klebsiella or Staphylococcal pneumonia</td>
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<td>Lung abscess</td>
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<tr>
<td>Septic emboli</td>
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<tr>
<td>Autoimmune</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Environmental exposures</td>
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<tr>
<td>Silica</td>
</tr>
</tbody>
</table>

The hypothetical etiology of WG is attributed to combinations of infectious, genetic, or environmental factors; however, efforts in identifying specific factors have proved to be difficult. The disease is equally distributed between men and women, presenting most commonly among the fourth and fifth decades of life.

The initial presentation of WG may be followed by an indolent, mild, or aggressive illness. Serum ANCA levels are seen to vary with the extent, severity, and activity of the disease. A limited form of the disease can restrict itself primarily to the lungs and is less likely to be ANCA positive, but this form may still eventually progress to the kidneys. Poorer survival is associated with older age and the need for dialysis.

Treatment of WG has advanced greatly since the disease was first described in 1936, when 1-year mortality was 100% with median survival of 5 months. Treatment with corticosteroids in the 1960s procured a median survival time of 8 months. The most significant medical breakthrough was the introduction of cyclophosphamide in the early 1970s that prolonged survival and relieved symptoms.

Overall, the treatment plan is two-fold: to induce remission in patients with active WG and to maintain remission once the goal has been achieved. The strategy in treating WG is primarily immune suppression given the inflammatory nature of the disease. Patient symptoms, disease activity, organ involvement, and lab test results are all determinants of a patient’s particular treatment plan. In severe WG with kidney involvement, cyclophosphamide and prednisone are generally prescribed, providing symptom relief in 91% of patients and inducing remission in 75% of patients. Due to the immunosuppressive nature of cyclophosphamide, it is preferred to switch to methotrexate or azathioprine after three to six months. Induction can be achieved in patients with mild disease with methotrexate and prednisone. During treatment, prophylactic therapy with Septra should be used to prevent Pneumocystic carinii pneumonia. Septra has also been associated with a decreased recurrence of WG.
presence of renal failure in a WG patient increases the risk of end-stage renal disease and mortality. For patients with creatinine over 500 µmol/L, plasma exchange has been shown to reduce this risk.\(^{13}\)

Even with treatment, WG can recur or maintain a low activity level in 60-80% of patients, leading to organ damage and chronic morbidity.\(^2\,^{14}\) Important risk factors for relapse were C-ANCA positivity and disease within the lower or upper respiratory tracts.\(^{15}\) Overall mortality for WG patients is four times the rate of the mortality of the general population.\(^{16}\) Most (93%) of the morbidity and mortality was due to disease-related activity rather than treatment-related causes.\(^9\)

Table 3. Key Points

- Wegener’s granulomatosis is a complex vasculitis with many potential systemic manifestations
- Suspect alternate etiologies in suspected cases of pneumonia that does not resolve with multiple antibiotics
- Goals of management are induction and maintenance of remission
- The patient on immunosuppressants for WG should be given prophylaxis and be vigilant for infections
- Reduce cardiac risk factors as vasculitic diseases increase the risk of an adverse cardiovascular event

Conclusion

WG is a systemic vasculitis with many potential clinical manifestations and is challenging to manage in the clinic. The diagnosis of WG has potentially devastating impacts on patients’ lives given the high risks of organ damage and recurrence of the disease. Treatment of WG reduces mortality and morbidity but does not eliminate these risks altogether. Consequently, patients should be given regular follow-up to monitor disease remission and organ function.

References


Inspiration

Location: Victoria Hospital in London, ON.
Program: Non-credit elective.