Microscopic polyarteritis: a forgotten aetiology of haemoptysis and rapidly progressive glomerulonephritis

Scott Zashin, Ron Fattor, Don Fortin

Abstract
A 76 year old white woman died from massive pulmonary haemorrhage nine days after she was admitted to Parkland Memorial Hospital for evaluation of haemoptysis and rapidly progressive glomerulonephritis. The differential diagnosis of haemoptysis with rapidly progressive glomerulonephritis is presented with particular emphasis on Wegener's granulomatosis and microscopic polyarteritis. Necropsy showed a small vessel necrotising vasculitis associated with a focal segmental necrotising glomerulonephritis consistent with microscopic polyarteritis.

Case report
A 76 year old white woman was admitted to the hospital for evaluation of fevers, patchy pulmonary infiltrates, and worsening renal function; she expired on the ninth hospital day.

She had been well until two months before admission to a hospital in Beaumont, Texas with fevers to 38-39°C, haemoptysis, oral ulcers, epistaxis, nasal congestion, and dyspnoea. The admission chest x ray showed a right upper lobe posterior segment cavitary infiltrate. Treatment was started with cefuroxime and she was treated parenterally for 10 days. Her sputum culture grew Klebsiella pneumoniae. The following evaluation was made: white blood cells 16 9-25 0x 10^9/l with 12-15% eosinophils, packed cell volume 0.3, platelets 613x10^9/l, urine analysis—sp gr 1.005, pH 6.5, no protein, 2+ blood with two to seven red blood cells/high powered field, creatinine 53-133 mmol/l, protein 71 g/l, albumin 35 g/l, serum aspartate transaminase 38 IU/l, alkaline phosphatase 275 IU/l, CH_50 normal, antinuclear antibody titre 1/80, thyroid function tests normal, erythrocyte sedimentation rate 115 mm/h. A chest computed tomographic scan was performed showing patchy ill defined confluent infiltrative changes in both mid and upper lung fields.

Bronchoscopy was performed on 26 August 1987, which showed mild interstitial fibrosis and chronic inflammation. The bronchial washings were negative for malignant cells. Multiple acid fast smears were negative.

Her fever subsequently defervesced and she remained afebrile for 48 hours. Her discharge chest x ray showed no change in infiltrates. She presented at follow up on 22 September 1987 with complaints of fevers for 14 days, with dependent left lower extremity oedema and arthralgias. She was transferred to this hospital for further evaluation.

Drugs on admission included famotidine and a stool softener. She denied smoking or alcohol intake. Her physical examination at the time of admission on 8 October 1987 was normal except for multiple purpuric macules, petechial lesions around paronychiae of fingers and plantar aspects of feet. Her chest x ray showed a right middle lobe opacity silhouetting the right heart.

Laboratory test results included creatinine 513 mmol/l, protein 59 g/l, albumin 28 g/l, white blood cells 21x10^9/l with 90% platelets, 6% lymphocytes, 3% monocytes, 1% eosinophils, packed cell volume 0.3, urine analysis—red blood cells too numerous to count, many white blood cells, white blood cell cast with 2+ protein.

At the time of admission three sets of blood cultures were drawn, which returned growing Staphylococcus epidermidis in one of six bottles. Biopsy of the purpuric lesions showed 'leucocytoclastic vasculitis'. On the third hospital day she received a bolus of 1.8 g methylprednisolone sodium succinate as she continued to show a rising creatinine concentration (now 539 mmol/l) with a persistent active sediment. Other laboratory results returned at that time were rheumatoid factor 85-9 IU/ml, C4 186 mg/l, C3 1 02 g/l, antinuclear antibody test negative, erythrocyte sedimentation rate 98 mm/h, total serum iron 220 μg/l, total iron binding capacity 163 mg/l, hepatitis B surface antigen non-reactive. A renal biopsy performed on 13 October 1987 showed that two of six glomeruli seen were crescents. The immunofluorescence showed deposits of IgG, IgM, and C3. She then received cyclophosphamide 100 mg and prednisolone 120 mg both by mouth every day beginning 15 October 1987. She remained stable until 4 pm on the 16 October 1987 when she was found to have haemoptysis, measured as 1/2 cup. Her examination showed marked tachypnoea (respiratory rate 40/min). An arterial blood gas obtained while the patient was receiving 2 litres of oxygen by nasal cannula showed pH 7.27, PCO_2 5.5 kPa, PO_2 6.2 kPa, which improved with 100% oxygen supplementation by Venturi mask to pH 7.22, PCO_2 6.4 kPa, PO_2 8.7 kPa. She was intubated and underwent emergency fiberoptic bronchoscopy. The bleeding source was felt to be the right upper lobe, but blood was present in all airways. During the bronchoscopy she developed massive haemoptysis and became asystolic. Cardiopulmonary resuscitation was started, but she died.

A postmortem examination was performed.

Necropsy
Principal necropsy findings in this patient involved the lungs and kidney.
LUNGS
Gross examination of the lungs showed intense congestion of all lobes. Examination of the lung at high magnification showed focal areas of alveolar wall thickening with associated necrosis and acute inflammation. All the pulmonary vessels were reviewed. A rare, degenerating vessel could be identified in such areas, although owing to disruption, it was not possible to determine whether the vessel was a vein or an artery. One or two of these necrotic areas were present in each lung section. There was no evidence of a granulomatous process. Special stains (tissue Gram stain and Gomori’s methenamine silver, with verified positive controls) were performed for bacterial and fungal micro-organisms; both of these stains were negative.

KIDNEYS
The most notable finding in the cortex was seen in the residual fraction of non-sclerotic glomeruli. Approximately 90% of all these glomeruli showed a global and segmental necrotising and proliferative glomerulitis. Occasional crescents were seen, though most glomeruli were remarkable only for the necrotising proliferative glomerulitis. Immunofluorescence studies on the renal biopsy specimen obtained before death showed only minimal granular deposits of IgG. There was no evidence of IgA. The tubules of both kidneys showed mild focal dilatation.

DIAGNOSIS
Microscopic polyarteritis.

Discussion
The differential diagnosis in this patient with haemoptysis and rapidly progressive glomerulonephritis is long (table 1). Yet the most likely diagnosis was either Wegener’s granulomatosis or microscopic polyarteritis.

Wegener’s granulomatosis is characterised by glomerulonephritis and by a necrotising granulomatous vasculitis of the upper and lower respiratory tract. Fauzi and his group at the NIH have accumulated a large series of patients. In their prospective study of 85 patients there was a 1.6:1 male to female ratio, the mean age of disease onset was 40 with a range of 14-75 years, and the mean duration from the time of symptoms to presentation was 8-3 months. The most common presenting complaint was sinusitis with severe rhinorrhoea or nasal obstruction (57/85). Otitis, secondary to obstruction of the eustachian tubes, was also common (21/85). Epistaxis was seen in only 9/85 of patients.

Pulmonary complaints were prevalent. Chest radiographs showed 60/85 presenting with an infiltrate, some with cavitation. The characteristic nodules of Wegener’s granulomatosis with or without cavitation were seen less frequently.12 13 It should be noted, however, that radiographic abnormalities may occasionally be fleeting.14 Haemoptysis was seen in only 15/85 of patients.12 Yet, in a series of patients with Wegener’s granulomatosis at Hammersmith Hospital haemoptysis was apparent in 21/53 of patients, with a high mortality (5/53) in the first two weeks.15 Thus the low incidence of haemoptysis in the NIH group may be due to the reasons for which their patients were referred.

Skin lesions were uncommon on initial presentation, but typical ulcerative or papular lesions were present in more than 38/45 of patients at some time in their course15; leukocytoclastic vasculitis was unusual.

Laboratory investigation shows that the erythrocyte sedimentation rate is characteristically very high. A normochromic/normocytic anaemia and leucocytosis are also common. Renal abnormalities include increased plasma creatinine, haematuria, and, less frequently, red cell casts. Rheumatoid factor was measured in 44 patients and was positive in 27.12 14 16

Although granulomatous necrotising vasculitis can be seen in biopsy specimens of the skin, sinus, or kidney, the lung has the greatest yield.17 Biopsy of a lesion in the nasopharynx can often provide a diagnosis if an adequate specimen consisting of deep tissue, and not just superficial necrotic tissue, is obtained.

Renal biopsy specimens are most commonly characterised by a focal segmental necrotising glomerulonephritis.18 Crescent formation is seen during rapidly progressive renal failure. Findings showing extraglomerular necrotising vasculitis are rare.17 Although the clinical presentation of our patient is compatible with Wegener’s granulomatosis, the diagnosis was microscopic polyarteritis.

Published work on microscopic polyarteritis is scarce and confusing because it is commonly included in series of hypersensitivity vasculitis and sometimes in series of classic polyarteritis. The term microscopic polyarteritis is best used to describe a patient with evidence of a small vessel vasculitis associated with a rapidly progressive glomerulonephritis clinically and a focal segmental necrotising glomerulonephritis pathologically. Excluded are patients with other diseases associated with a small vessel vasculitis and necrotising glomerulonephritis (Wegener’s granulomatosis, Schönlein-Henoch purpura, mixed cryoglobulinaemia, hypocomplementaemic vasculitis, and hypersensitivity vasculitis secondary to neoplasms).19

The Hammersmith group recently published

Table 1: Differential diagnosis of rapidly progressive glomerulonephritis and haemoptysis

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td></td>
</tr>
<tr>
<td>Bacterial endocarditis</td>
<td></td>
</tr>
<tr>
<td>Legionnaires’ disease</td>
<td></td>
</tr>
<tr>
<td>Streptococcal pneumonia</td>
<td></td>
</tr>
<tr>
<td>Bronchogenic carcinoma</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
</tr>
<tr>
<td>Goodpasture’s syndrome</td>
<td></td>
</tr>
<tr>
<td>Idiopathic rapidly progressive glomerulonephritis</td>
<td>(with and without immune complexes)</td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
</tr>
<tr>
<td>Classic polyarteritis nodosa</td>
<td></td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td></td>
</tr>
<tr>
<td>Microscopic polyarteritis</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity vasculitis</td>
<td></td>
</tr>
<tr>
<td>Schönlein-Henoch purpura</td>
<td></td>
</tr>
<tr>
<td>Mixed cryoglobulinaemia</td>
<td></td>
</tr>
</tbody>
</table>
a large series describing patients who fit the
diagnosis of microscopic polyarteritis.9 The
patient profile of this group is similar to the
profile of those afflicted with Wegener’s granu-

lomatosis. Of the 34 patients in the series, two
out of three were male. All but two were white.
The average age was 50 years with a range of
14–73. The mean duration from the time of
symptoms to presentation was 3–7 months.

The onset of disease is often preceded by
constitutional symptoms. Purpura was com-
monly present and biopsy of skin lesions showed
predominantly leukocytoclastic vasculitis.

Pulmonary manifestations were dominated
by haemoptysis and alveolar haemorrhage as
defined by a typical alveolar infiltrate and a
raised transfer factor of the lung for carbon
monoxide (TLCO). TLCO is the diffusion capa-
city corrected for the alveolar volume.19 A
raised value is felt to be a sensitive indicator of
alveolar haemorrhage. Pulmonary infiltrates
without infection were not seen.

Nasopharyngeal involvement was common
and included oral ulcers, sinusitis, and epistaxis.
Abdominal involvement was also common,
though this was not present in our patient.
Finally, cardiovascular and neurological abnor-
malities were rare.

The laboratory investigations of all patients
showed a raised erythrocyte sedimentation rate,
anaemia, an abnormal creatinine concentration,
and microscopic haematuria. Most had granular
or red cell casts. Other significant laboratory
results included a high prevalence of leucocytosis
with neutrophilia and thrombocytosis. Rheu-
matoid factor was positive in 41%.

If renal studies are excluded most of these
laboratory abnormalities are non-specific and
found to a greater or lesser extent in all types of
vasculitis. An exciting, prospective controlled
study recently published in the Lancet showed
that autoantibodies against neutrophil cyto-
plasmic antigens were specific and sensitive for
both Wegener’s granulomatosis and microscopic
dysgranulomatous vasculitis.29 Controls were normal patients
and those with pulmonary-renal syndromes.
Nevertheless, more patients need to be studied
before this test can be used as an important
diagnostic aid in clinical medicine.

Renal biopsy specimens were obtained from
94% of patients. A focal segmental necrotising
glomerulonephritis was found in all patients.9
Crescents were seen in 88%.

Yet, we are told that no evidence of a focal
segmental necrotising glomerulonephritis was
found in our patient. Because 100% of patients
with microscopic polyarteritis in a previous
study had this finding it might be thought that
microscopic polyarteritis could be excluded as a
diagnosis. The renal biopsy specimen was in-
adequate, however, as only six glomeruli were
seen. Thus the characteristic lesion was not
evident until necropsy.

Direct immunofluorescence staining was per-
formed on biopsy specimens of 20 patients with
microscopic polyarteritis and showed minimal
deposition of C3 and even less deposition of
IgG.9 This lack of significant immunofluores-
cence is consistent with all types of vasculitides,
excluding Schönlein-Henoch purpura.

An open lung biopsy would probably be
necessary to distinguish Wegener’s granuloma-
tosis from microscopic polyarteritis, however.
Still, the distinction between these two entities
was only of academic importance as the major
consideration was treatment of rapidly progres-
sive glomerulonephritis.

Although no controlled trials have been done,
the standard treatment for systemic necrotising
vasculitis with internal organ involvement is
with a combination of cyclophosphamide and
prednisone.8 The cyclophosphamide should be
given in a dose of 1.5–2 mg/kg daily by mouth.
If there is fulminant disease a dose of up to
4 mg/kg daily can be given for the first three
days and then cut back to 2 mg daily. If the
patient cannot tolerate drugs by mouth or there
is intestinal involvement, the drug is given
intravenously. The dose may be increased by 25
mg every two weeks until a clinical response
occurs or toxicity develops. The drug should be
continued for one year after a remission
has occurred. The goal of therapy is to suppress
disease activity while keeping the white blood
cell count above 3.5 × 109/l to decrease the risk
of infection.

Azathioprine is an alternative agent, but in
the NIH experience it is less effective than
cyclophosphamide.21 Still, it may be useful in
patients who cannot tolerate the side effects
of cyclophosphamide, such as leucopenia, hae-
morrhagic cystitis, or gonadal dysfunction.
Both drugs take at least 10 days before any
effect on disease activity is seen. Consequently,
prednisone is added for immediate anti-
inflammatory and immunosuppressive effects.
The recommended dose is 1–2 mg/kg daily in
three to four divided doses. The divided dose
early in treatment produces the maximum
therapeutic response as the effect of prednisone
is at a peak after four hours. After two weeks of
continuous treatment the drug can be given as a
single morning dose and withdrawn over three
months.

Pulse therapy—that is, 1–2 g of methyl-
prednisolone given intravenously over 30
minutes—is often used in severe cases of vasculi-
is. Although there are no data at present
showing a benefit over high dose prednisone
taken by mouth, it is reasonable to use this
regimen in disease not responding to conven-
tional steroid doses or in life threatening disease.

In addition to treating the kidney disease,
high dose prednisone and pulse therapy have
been successfully used to treat pulmonary hae-
morrhage.22 23

The combination of cyclophosphamide and
prednisone has been very effective in treating
Wegener’s granulomatosis. Before this treat-
ment the average one year survival was less than
20% with a mean of five months.24 With the
aforementioned regimen 93% of patients experi-
enced a remission with a four year survival of
88%.12

Less success has been obtained in micro-
scopie polyarteritis. The five year actuarial
survival was 65% in the Hammersmith study.9
At the NIH the increased mortality compared
with that for patients with Wegener’s granulo-
matosis might have been secondary to the
Table 2: Summary

<table>
<thead>
<tr>
<th>Clinical finding</th>
<th>Wegener’s granulomatosis</th>
<th>Microscopic polyarteritis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Rapidly progressive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>glomerulonephritis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nasopharyngeal</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucocytoclastic</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>vasculitis (excluding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>infection and</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>haemorrhage</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

inherent diseases because azathioprine and not cyclophosphamide was used as the principal mode of treatment, or might have been due to the patient population.

Patients with microscopic polyarteritis and pulmonary haemorrhage had a poor prognosis. Of the 10 patients with this complication, three died in the first two weeks. These deaths represented 60% of the deaths during this period. Because pulmonary haemorrhage is an indicator of such a poor prognosis it is doubtful that any alteration in treatment would have changed the eventual outcome of this case.

In summary, the presentation of this patient is consistent with both Wegener’s granulomatosis and microscopic polyarteritis (table 2). In addition to their association with rapidly progressive glomerulonephritis and haemoptysis, both present with constitutional symptoms and nasopharyngeal involvement. Yet, because of the presence of leucocytoclastic vasculitis, a common finding in microscopic polyarteritis, and the absence in our patient on presentation to Parkland of radiographic findings consistent with Wegener’s granulomatosis, microscopic polyarteritis represented the best clinical diagnosis. This diagnosis was confirmed by pathological evidence of a focal and segmental necrotising glomerulonephritis, a small vessel vasculitis, and the absence of granulomas.