CASE REPORT

Vasculitis reminds us that 'Ockham's razor' may still apply in the elderly

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SUMMARY

A 76-year-old woman with a history of stage IV chronic kidney disease and hypertension was admitted to the hospital for progressive weakness and acute on chronic kidney injury. She was found to have anaemia requiring transfusion. On the evening of admission, she had worsening respiratory status with subsequent diagnosis of a non-ST-elevation myocardial infarction, pulmonary oedema on chest x-ray presumed to be a result of heart failure, and a possible transfusion reaction. A kidney biopsy performed as part of her ongoing nephrology evaluation revealed granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis). Subsequent bronchoalveolar lavage confirmed diffuse alveolar haemorrhage as the explanation for her anaemia and respiratory decline. She underwent immunosuppressive therapies and initiated dialysis, but subsequently chose hospice care and died 2 months after her diagnosis.

BACKGROUND

Granulomatosis with polyangiitis (GPA) requires early diagnosis and treatment to prevent severe complications including multiorgan failure and death. The challenge is that GPA is rare and its symptoms and signs overlap with more common diagnoses. GPA is present in an estimated 130 people/100 000 in the UK or 3 people/100 000 in the USA.¹⁻³ The disease can initially involve almost any system and often has multisystem involvement.² Presenting symptoms overlap with many infectious or malignant aetiologies and can include fatigue, arthralgias and generalised weakness. The diagnosis is often made with serum testing for antineutrophil cytoplasmic antibodies (ANCA), although the false-positive and false-negative rates are high.² Ultimately, biopsy is needed to make a definitive diagnosis and consultation with an appropriate specialist is recommended.² It is important to consider vasculitis in the differential diagnosis of patients presenting with problems involving multiple systems, especially in the setting of rapidly progressing renal failure.

CASE PRESENTATION

A 76-year-old woman with a history of stage IV chronic kidney disease and hypertension was admitted for progressive weakness and acute on chronic kidney injury. She did not complain of any symptoms aside from weakness that was most notable when trying to stand to get out of bed. She was requiring more assistance over the past week

and after seeing her nephrologist was referred to go to the hospital for evaluation.

Other medical history of note was a diagnosis of anaemia requiring transfusion as an outpatient 1 month prior to admission. Iron studies suggested a combination of iron deficiency and anaemia of chronic disease. She also had a remote history of hyperthyroidism for which she was treated with radioiodine ablation, a small atraumatic intracerebral haemorrhage 4 years prior to the admission and chronic sinusitis. She had no known autoimmune disease and no identified cause for her atraumatic intracerebral haemorrhage.

Her physical examination was remarkable only for symmetric 4/5 muscle strength in all muscle groups tested. Laboratory evaluation was significant for anaemia (haemoglobin 6.9 g/dl). Her chest x-ray showed consolidation in her left lower lobe suspicious for pneumonia (figure 1). The anaemia and pneumonia were presumed to be the reasons for her progressive fatigue and weakness. She was given three units of packed red blood cells and started on antibiotics on admission. On the evening of admission she had worsening of her respiratory status requiring 2 litres of nasal cannula oxygen support. Evaluation identified elevated troponin levels, worsening bilateral airspace disease on chest x-ray and severely reduced systolic function on echocardiogram. The clinical picture was consistent with a non-ST elevation myocardial infarction (NSTEMI) with heart failure leading to pulmonary oedema. She was given furosemide and started on intravenous heparin therapy while awaiting cardiac catheterisation.

Figure 1 Chest x-ray revealing bilateral pulmonary airspace disease presumed to be a pneumonia or pulmonary oedema due to her non-ST elevation myocardial infarction.

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Her anaemia did not fully respond to transfusion although there was no obvious source of bleeding, which was concerning given that she was on heparin therapy. A renal biopsy performed 2 days earlier revealed granulomatosis with polyangiitis (previously called Wegener's granulomatosis).

INVESTIGATIONS

The key to determine the final diagnosis was the nephrology investigation that had been ongoing. She had been diagnosed with chronic kidney disease 6 years previously with no clear aetiology aside from her hypertension. A renal ultrasound showed bilateral atrophic kidneys 2 years prior and a renal angiogram showed mild bilateral renal artery stenosis that did not explain the full extent of her disease or the rapid progression. She previously had a weakly positive antinuclear antibody (ANA, titre 1:80), normal ANCA and normal complement levels. Her renal function on admission had worsened from baseline, but because of improvement with hydration it was presumed to be pre-renal. The nephrologist happened to perform a biopsy on this admission as part of the ongoing evaluation, but even when initial results showed possible crescentic glomerulonephritis the suspicion was low because of the prior normal autoimmune evaluation. Repeat ANCA testing was performed and returned positive for p-ANCA (titre 1:320) and positive for antimyeloperoxidase antibody (anti-MPO). The final biopsy report confirmed crescentic, pauci-immune, necrotising glomerulonephritis suspicious for granulomatosis with polyangiitis.

Another interesting nuance of her case was the anaemia evaluation. She had iron studies consistent with a combination of anaemia of chronic disease and iron deficiency months prior to admission. She had normal stool testing for occult bleeding to evaluate the iron deficiency, but no prior colonoscopy. Her reticulocyte response was insufficient based on the level of anaemia (low reticulocyte index) which could have been because of her renal disease, but further investigation for bone marrow disease revealed normal serum and urine protein electrophoreses (SPEP and UPEP). She had received outpatient transfusions for severe anaemia (haemoglobin level less than 7 g/dl), and her last transfusion was 1 month earlier at which time she was started on erythropoietin. It was not initially clear why her haemoglobin dropped again within 1 month of these interventions. The aetiology was clearer after the renal biopsy, and the diagnosis of diffuse alveolar haemorrhage was confirmed by bronchoalveolar lavage.

DIFFERENTIAL DIAGNOSIS

The patient's worsening respiratory status on the evening of admission was most concerning for an NSTEMI with significant pulmonary oedema from heart failure. Other possibilities included a transfusion reaction, aspiration pneumonitis or acute respiratory distress syndrome (ARDS) because of infection or other inflammatory process.

The most likely reason for bilateral airspace disease in this patient was acute decompensated heart failure owing to an NSTEMI based on the elevated cardiac enzymes and decreased systolic function. The patient had no history of coronary artery disease, but it was assumed that this was ischaemic heart disease by the primary team as well as the cardiology consultant. She did not improve with furosemide, and she did not endorse chest pain at any point. The approach was reasonable, but alternative diagnoses needed to be considered given her worsening anaemia and respiratory status.

She certainly could have been having a transfusion reaction, aspiration pneumonitis or ARDS, although management would

have been supportive including antipyretics, antibiotics if indicated and intubation if she developed respiratory failure. Diffuse alveolar haemorrhage was not considered at the time as it usually presents with haemoptysis, but including it in the differential of a patient with respiratory decline and anaemia is important since management usually involves glucocorticoids or more advanced interventions when severe.

TREATMENT

The patient was transferred to the intensive care unit (ICU) after emergent bronchoalveolar lavage confirmed diffuse pulmonary alveolar haemorrhage. She required intubation for 4 days owing to worsening respiratory status. She underwent 5 days of plasmapheresis along with high-dose glucocorticoid therapy and an initial dose of cyclophosphamide. Dialysis was initiated during the hospitalisation. She improved prior to transfer out of the ICU, but developed pancytopenia requiring filgrastim.

OUTCOME AND FOLLOW-UP

She stabilised for discharge to a skilled nursing facility. Close nephrology follow-up was arranged, and she was discharged on a prolonged steroid taper. She returned 2 weeks later with a lower gastrointestinal (GI) bleed thought to be related to severe constipation with a rectal fissure and possible haemorrhoids. She declined further evaluation and treatment aside from a bowel regimen for the GI bleed as she preferred hospice care. She died peacefully according to her friends and family at her nursing facility 1 month after this discharge, 2 months after her diagnosis of GPA.

DISCUSSION

Medical training often emphasises the practical use of Ockham's famous principle ('Ockham's razor'): the simplest explanation with the fewest assumptions should be favoured. Taught as a corollary is that Ockham's razor usually does not apply to elderly patients since they have accumulated multiple diagnoses. This case report reminds us that considering a unifying diagnosis even in elderly patients is still important. The patient's presentation included many common conditions: anaemia, renal failure, NSTEMI and pulmonary disease. When stepping back to examine the entire clinical picture, including her history of chronic sinusitis, it is possible to attribute all of her medical problems to the diagnosis of vasculitis.

Diagnosing small vessel vasculitides such as GPA is difficult because of the wide range of presentations. Patients may present with constitutional symptoms such as fevers, myalgias, fatigue and arthralgias that leave a broad differential diagnosis: infectious, autoimmune, neoplastic and more. GPA typically has pulmonary and renal involvement that helps differentiate it from the other small vessel vasculitides (table 1). Pulmonary involvement is found in over 90% of patients and can manifest in a variety of ways including sinusitis, stridor because of tracheal inflammation or lung infiltrates.^{4 5} Renal involvement is typically a glomerulonephritis that develops after the initial presentation. Only 20% of patients present with glomerulonephritis which strengthens the retrospective argument that our patient may have had GPA for months to years prior to the diagnosis.^{4 5} Cutaneous or neurological involvement is possible and manifests as purpura, skin nodules or peripheral neuropathy. The pulmonary haemorrhage in this patient is somewhat atypical and warranted more aggressive treatment with plasmapheresis, methylprednisolone and cyclophosphamide.

Table 1 Comparison of clinical characteristics of small vessel vasculitides:

Small vessel vasculitides	Clinical and diagnostic features*†
ANCA associated	
Churg-Strauss syndrome	Asthma and eosinophilia, necrotising vasculitis, predominately antiMPO-ANCA
Drug induced	Exposure to drug within 7–21 days (common implicated medicines include penicillin, aminopenicillins, sulfonamides, allopurinol, thiazides, quinolones, hydantoins and prophylthiouracil) ⁴
Granulomatosis polyangiitis (formerly Wegener's)	Upper respiratory tract disease, renal disease, predominately antiproteinase 3-ANCA
Microscopic polyangiitis	Pulmonary and renal disease, predominately MPO-ANCA
Non-ANCA associated	
Immune-complex vasculitis:	Features of specific diagnosis:
▶ HSP	▶ Abdominal pain, glomerulonephritis, purpura, arthralgias. IgA immune-complex vasculitis (HSP)
▶ Rheumatoid vasculitis	▶ Signs and symptoms of rheumatoid arthritis or systemic lupus erythematosus
▶ Lupus vasculitis	
▶ Drug-induced immune-complex vasculitis	▶ Recent exposure (usually within days to weeks) to new medication or vaccine.
▶ Sjogren's vasculitis	▶ Dry skin and mucous membranes, positive anti-SSA/Ro or anti-SSB/La.
▶ Cryoglobulinaemia vasculitis	▶ Skin lesions, arthralgias, renal involvement and serum cryoglobulins. May have RF,† Hep C† and low complement (specifically C4) (cryoglobulinaemia)
▶ Hypocomplementaemia vasculitis	▶ Low complement levels, urticarial rash. May have joint, kidney and/or GI tract involvement (hypocomplementaemia)
▶ Infection-induced immune-complex vasculitis	▶ Recent infection
Inflammatory bowel disease vasculitis	Symptoms of inflammatory bowel disease
Paraneoplastic vasculitis	Weight loss, night sweats

*All small vessel vasculitides may be associated with constitutional signs and symptoms such as fevers, malaise, muscle and joint aches.

†All listed vasculitides may have variable involvement of different systems. Most typical presenting symptoms and diagnostic characteristics are listed here.

ANCA, antineutrophil cytoplasmic antibodies; GI, gastrointestinal; Hep C, hepatitis C; HSP, Henoch-Schönlein purpura; IgA, immunoglobulin A; MPO, myeloperoxidase.

Unfortunately, there is no single laboratory test to exclude the diagnosis of vasculitis or GPA, and even the useful tests have a lower sensitivity. The initial panel of labs to aid in diagnosing small vessel vasculitides may include erythrocyte sedimentation rate (ESR), c reactive protein (CRP), complete blood count (CBC), and urinalysis to assess for haematuria and proteinuria.² If suspicion is high because of multiple system involvement for many weeks (especially pulmonary and renal), or the patient has elevated ESR or CRP, further evaluation should include hepatitis B and C serologies, ANCA, ANA, cryoglobulins, complement levels and rheumatoid factor.^{2–4} An international consensus statement by clinical pathologists recommends ANCA testing only when specific clinical criteria are present (box 1). An indirect immunofluorescence (IIF) should be used as the initial screen for ANCA, followed by ELISA if the IIF is positive.^{2–6–7} The most specific lab test for GPA is ANCA (98%) although the sensitivity ranges from 57% to 74% depending on the laboratory and type of test.⁸ Use of both IIF and ELISA testing increases sensitivity.⁷ The test may be negative early in the

disease or if the disease is inactive which is why some groups have argued for limiting ANCA testing to those with specific clinical conditions (box 1). Ultimately tissue biopsy of an affected organ is the gold standard for confirming the diagnosis of GPA when possible. Prompt diagnosis is important to prevent rapid progression which has a high mortality. Timely initiation of immunosuppressive therapies can result in the disease becoming a chronic illness, but it takes an astute physician to consider GPA in the differential diagnosis.

Box 1 Clinical characteristics which warrant antineutrophil cytoplasmic antibodies testing

- ▶ Chronic destructive airways disease
 - ▶ Mononeuritis multiplex
 - ▶ Pulmonary nodules
 - ▶ Pulmonary–renal syndrome
 - ▶ Rapidly progressive glomerulonephritis
 - ▶ Retro-orbital mass
 - ▶ Subglottic stenosis of the trachea
 - ▶ Vasculitis of the skin with systemic complaints
 - ▶ Any condition that resembles systemic vasculitis
- Adapted from Savage *et al.*⁶

Learning points

- ▶ Vasculitis can mimic many common conditions, but can provide a unifying diagnosis when present.
- ▶ Consider bronchoalveolar haemorrhage in patients presenting with pulmonary oedema and anaemia.
- ▶ Consider granulomatosis with polyangiitis (GPA) in the differential diagnosis of patients with pulmonary and renal diseases.
- ▶ Tissue biopsy is the gold standard to diagnose GPA, but when clinical suspicion is high consider antineutrophil cytoplasmic antibodies testing to aid in diagnosis.

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