ANCA associated vasculitis

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What you need to know

• Consider ANCA associated vasculitis (AAV) in people with chronic systemic symptoms and evidence of renal, pulmonary, ear, nose, and throat, ophthalmic, or peripheral nerve disease
• Perform urinalysis in people presenting with persistent systemic symptoms and in those with specific features of vasculitis (scleritis, chronic dyspnoea, cough, haemoptysis, foot drop) because these individuals have a high probability of multi-system disease
• Patients with haemoptysis plus other features of AAV warrant same day hospital assessment to evaluate for pulmonary haemorrhage

Nicola, 44, goes to her general practitioner with a one month history of fatigue and night sweats. Physical examination is unremarkable. The duration of her symptoms prompts her GP to consider systemic inflammatory disease. Urinalysis is positive for blood and protein, and blood tests show new renal impairment (serum creatine 327 μmol/L, estimated glomerular filtration rate (eGFR) 13 mL/min/1.73m²) and evidence of an inflammatory response (C-reactive protein 50 mg/L, haemoglobin 103 g/L, platelets 461 x 10⁹/L, albumin 33 g/L). Nicola is referred urgently to her local renal unit and undergoes kidney biopsy and testing for anti-neutrophil cytoplasmic antibodies (ANCA). She is diagnosed with ANCA-associated vasculitis.

What is ANCA associated vasculitis?

ANCA associated vasculitis (AAV) is an umbrella term for a group of multi-system autoimmune small vessel vasculitides that can present at any age and affect 20-25 people per million per year in Europe. 1 A typical GP practice with 8000 patients can expect to see one new case approximately every five years. AAV diseases include microscopic polyangiitis, granulomatosis with polyangiitis (GPA, previously “Wegener’s granulomatosis”), and eosinophilic granulomatosis with polyangiitis (EGPA, previously “Churg-Strauss syndrome”). 2 The conditions are characterised by formation of granulomas and inflammation of small arteries, arterioles, venules, and capillaries. 1 Inflamed vessels may rupture (for example, causing alveolar haemorrhage or a purpuric rash) or become occluded (for example, causing segmental glomerular infarction), giving rise to a broad array of clinical symptoms and signs related to a systemic inflammatory response, end organ microvascular injury, or the mass effect of granulomas.

What symptoms do patients develop?

AAV may present with constitutional symptoms suggestive of chronic inflammatory disease (fatigue, weight loss, fever, night sweats, myalgia, or polyarthralgia) or with specific features of end-organ involvement. Almost any part of the body can be affected, but the most commonly affected systems are the upper airways, lungs, kidneys, eyes, and peripheral nerves. Therefore, presenting symptoms include sinus pain, nasal discharge, or crusting, ear pain, or deafness (from upper airways involvement), cough, shortness of breath, wheeze or haemoptysis (from lung involvement), and painful, red eyes (from scleritis). Some patients may have weakness, numbness, or difficulty walking, but many patients do not mention these symptoms, and signs of peripheral neuropathy—such as foot drop or wrist drop—should be specifically sought on examination. A classic “vasculitic” purpuric skin rash is present in a minority of patients. Common presenting symptoms are listed in box 1.
misdiagnosed as refractory or frequently relapsing asthma.

...with shortness of breath and wheeze and is often initially attributed to more common diseases such as uncomplicated sinusitis, asthma, or scleritis. For example, EGPA may present but regarded as a manifestation of another disease. Why is it missed?

People with predominant myalgia may be misdiagnosed as having polymyalgia rheumatica and—because corticosteroid treatment partially treats AAV—correct diagnosis is delayed until the steroid dose is weaned and other symptoms emerge. Granulomatosis with polyangitis with cavitating lung lesions can be misdiagnosed as lung cancer.

Diagnosis can also be delayed or missed when symptoms in disparate organs are not recognised as manifestations of a single disease. A patient may attend separate clinics: ear, nose, and throat (for nasal crusting), ophthalmology (for scleritis), and neurology (for peripheral neuropathy) without anybody “joining the dots” between these symptoms. Indeed, a UK case-control study found that patients had frequent healthcare encounters in the months before a new diagnosis of GPA, with nearly 20% of patients attending two or more specialist clinic appointments in the year before diagnosis (compared to ~5% of controls).

Why does this matter?

There is a stark difference in patient outcomes when diagnosis is delayed or missed: untreated, only one in 10 patients survives beyond two years—a prognosis that is worse than most cancers. If promptly recognised, however, AAV responds well to immunosuppressive treatment. AAV can present at any age and affects all ethnicities; the incidence is over 70 is 80-90 per million per year. Several genetic and environmental risk factors have been identified, but most of the variation in incidence is accounted for by patient age. Incidence rises progressively with age until the mid-late 80s, so that the incidence in the population aged over 70 is 80-90 per million per year and consequently AAV is the leading cause of glomerulonephritis in this age group.

However, AAV can present at any age—including in childhood—and affects all ethnicities; the incidence is approximately the same in women and men. Environmental risk factors are absent in most cases but exposure to drugs such as cocaine, hydralazine, and propylthiouracil has been implicated.

Why is it missed?

Diagnosis of AAV is often delayed or missed because the condition has virtually no pathognomonic features, and most of the presenting symptoms are either general—and thus may be misdiagnosed as another systemic disease—or more specific but attributed to more common diseases such as uncomplicated sinusitis, asthma, or scleritis. For example, EGPA may present with shortness of breath and wheeze and is often initially misdiagnosed as refractory or frequently relapsing asthma. People with predominant myalgia may be misdiagnosed as having polymyalgia rheumatica and—because corticosteroid...
The second difficult scenario is AAV presenting as organ limited disease, without systemic symptoms. For example, most patients with isolated glomerulonephritis have no symptoms until renal failure advances to the point of uremia. Thus, consider AAV in patients with falling eGFR with blood and protein on urine dipstick even if they have no constitutional symptoms and full blood count and C reactive protein results are normal. The differential diagnosis of AAV includes cancer, chronic infection (particularly bacterial endocarditis), and other autoimmune conditions. Because of the difficulties in diagnosis, discuss patients with possible or suspected AAV early with a specialty service.

Investigations

Investigations can further support a diagnosis of AAV and refute the major differential diagnoses of infection and cancer. As in the case study, urinalysis can rapidly screen for renal involvement in a multi-system disease. Patients with haematuria or proteinuria in this context have a high probability of having AAV. This probability is 2% if the dipstick findings occur in isolation, rising to 85% if there is concomitant sinus and pulmonary disease.17 18

ANCA testing improves diagnostic certainty for patients with a high pre-test probability of disease.19 However, up to 10% of patients with small vessel vasculitis clinically test negative for ANCA. Conversely, false positive results can occur in the general population and in association with infections, malignancy, and autoimmune gastrointestinal and renal disease.4 Given this complexity, ANCA tests are not usually requested in primary care. Kidney or lung biopsies may be taken by specialty services to confirm a diagnosis of AAV or exclude differential diagnoses such as cancer.

How is it managed?

AAV is managed by a specialty service, which may be a rheumatology, renal, respiratory, or dedicated vasculitis service. It is treated with immunosuppressive therapies such as glucocorticoids, cyclophosphamide, rituximab, azathioprine, methotrexate, and mycophenolate mofetil. Adjunctive treatments aim to reduce the risk of infections—particularly pneumocystis, osteoporosis, diabetes, and cardiovascular disease.19

Case history outcome

Nicola was treated with glucocorticoids, cyclophosphamide, plasma exchange, and rituximab. Her renal function initially deteriorated before her disease entered remission, but she avoided the need for dialysis. She now enjoys a good quality of life and her renal function has improved and stabilised to a serum creatine of 188 μmol/L/eGFR 25 mL/min/1.73m². Without prompt consideration of a multi-system illness in primary care, Nicola would almost certainly have developed irreversible end stage renal failure within weeks.

Additional resources

• RCGP eLearning hosts 5 and 30 minute online learning modules aimed at improving the recognition and diagnosis of ANCA vasculitis in primary care https://www.thelaurencurrietwilightfoundation.org/gpcampaign/

A patient’s perspective

I initially visited my GP in August 2018 after feeling very tired and experiencing headaches and nausea. I had been having some night sweats but had self-diagnosed this as a peri-menopausal symptom. I was also caring for my mum who had terminal cancer, and my two kids alongside running a charity so put most of my symptoms down to stress and anxiety. I explained this to my GP who said he would like to check some blood tests, which surprised me. I thought he was just being thorough and fully expected the results to be fine. The next day he called to explain that I needed to be admitted to hospital as my kidneys were not working properly. My initial reaction was shock as I still felt relatively well; however, in hindsight, there were a few minor “warning signs” over the past year that I had ignored. These were very minor though, and it is worrying that there were not more obvious signs that something was wrong. I had no idea you could feel so well until things were so critical with your kidneys. After a few tests including a kidney biopsy, I was diagnosed with vasculitis. I was started on various treatments, including plasma exchange. I am now on lots of medication and have 6 monthly rituximab infusions to suppress my disease. I am back at work and although I have to take life a little slower, I am generally very well and feeling good. I will be forever grateful to my intuive GP who really listened to me and didn’t delay in testing me. This most likely saved me from dialysis and I can never thank him or the renal team enough for their swift care. I really hope this is a reminder to other doctors that testing early, with such minor symptoms, can be lifesaving.
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Figure

Fig 1 Clinical consequences of AAV. (a) Diffuse alveolar haemorrhage. (b) Nail fold infarction and splinter haemorrhages. (c) Nasal bridge collapse resulting from chronic, erosive inflammation in the upper airways. Delayed diagnosis can result in permanent disability/deformity and early mortality. Manifestations of advanced disease such as a “saddle nose” deformity are relatively rare but can still occur if a diagnosis of AAV is missed (these images are not directly related to the case study in this article).