

In the Beginning, it was Arthritis...

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A 20-year-old man presented with general fatigue for one month and migratory arthritis involving the metacarpophalangeal, proximal interphalangeal, elbow, and metatarsophalangeal joints associated with morning stiffness. He later showed bilateral eye redness and pain, and an ophthalmologist diagnosed bilateral iritis that rapidly improved with eye drops. The patient had no signs of urethritis and denied any prior episode of diarrhea. He had no significant personal or familial medical history. He never smoked and denied any alcohol or recreational drug use.

Laboratory investigations revealed hemoglobin level 123 g/L (normal, 140 g/L-180 g/L), leukocyte count $7.6 \times 10^9/L$ ($2.5 \times 10^9/L$ - $7.5 \times 10^9/L$), platelet count $491 \times 10^9/L$ ($150 \times 10^9/L$ - $400 \times 10^9/L$), erythrocyte sedimentation rate 33 mm/hr (< 15 mm/hr), C-reactive protein (CRP) level 86 mg/L (< 10 mg/L), serum creatinine level 66 $\mu\text{mol/L}$, alanine aminotransferase level 64 U/L (< 36 U/L) and alkaline phosphatase level 93 U/L (< 100 U/L). Rheumatoid factor (RF) was positive at 1:160. The patient was negative for antinuclear antibodies (ANA) and extractable nuclear antigens (ENA) as well as HIV and hepatitis B and C virus (HCV). Urine analysis gave normal results. Hand X-rays showed no erosions.

Diagnostic Work-up and Initial Management

The patient first sought medical care in a walk-in-clinic one month after the onset of the joint symptoms. He was given naproxen, which was initially helpful. After bilateral iritis developed, he was tested for anti-cyclic citrullinated peptide (anti-CCP) antibodies and HLA-B27, but both were negative. X-rays of the sacro-iliac joints were normal; however, because of the persistent arthritis, methotrexate (MTX) was started, with a working diagnosis of early rheumatoid arthritis (RA).

In the absence of anti-CCP antibodies, the diagnosis of early RF-positive RA was debatable. RF is not specific. Transient positivity can occur in patients with hypergammaglobulinemia or infections, including HCV infection or more sustainably, those with cryoglobulinemia or other autoimmune conditions with high titres of other auto-antibodies, such as anti-smooth muscle (autoimmune hepatitis) or antineutrophil cytoplasmic antibodies (ANCA). Almost all of these latter conditions can start with non-specific polyarthritis. Iritis is not a common symptom in ANCA-associated vasculitis but is found in a few patients. Hence, reactive spondyloarthropathy could

still be considered in this patient, which was not ruled out by the absence of HLA-B27.

However, one month later, cyanotic discolouration of the toes developed with numbness and tingling in the hands (in the right ulnar and both median nerve distributions), lateral side of the legs, and dorsum of the feet, mainly around the right medial malleolus; there was similarly weakness in hands and in the left big toe extensors. Electromyography with nerve conduction study confirmed the diagnosis of mononeuritis multiplex. At that time, the serum creatinine level had increased to 220 $\mu\text{mol/L}$, with blood 4+ and protein 3+ on urine analysis, and CRP level 86 mg/L. Chest X-rays were normal.

The clinical and biological findings no longer favoured RA or spondyloarthropathy, but more likely a medium-sized vessel vasculitis (*i.e.*, polyarteritis nodosa) or small-sized vessel vasculitis (such as an ANCA-associated vasculitis [AAV]). The presence of renal involvement with hematuria and proteinuria in the absence of high blood pressure suggested AAV more than polyarteritis nodosa. The presence of erythrocyte casts in the urine, suggestive of glomerulopathy (as opposed to an ischemic renal

injury in polyarteritis nodosa that usually does not cause casts), supported a diagnosis of AAV.

While waiting for ANCA test results, intravenous pulses of methylprednisolone (1 g/day for three consecutive days) were started. After renal ultrasonography, the patient underwent a kidney biopsy that demonstrated pauci-immune necrotizing crescentic glomerulonephritis. ANCA testing was positive, with a cytoplasmic-labeling pattern on indirect immunofluorescence and proteinase 3 (PR3)-specificity on enzyme-linked immunosorbent assay (ELISA). With this final diagnosis of anti-PR3 cANCA-positive and kidney-biopsy proven AAV (granulomatosis with polyangiitis [GPA] or microscopic polyangiitis [MPA]), additional induction treatments were considered, including an immunosuppressant and plasma exchange.

Diagnostic Discussion

AAV predominantly affects the respiratory tract and kidneys and includes GPA (formerly Wegener's granulomatosis), MPA, and eosinophilic granulomatosis with polyangiitis (also known as Churg-Strauss syndrome [EGPA]). A recent study in northern Saskatchewan showed a Canadian rate of 11.7 per million for GPA and MPA with biopsy-proven renal involvement.¹ Musculoskeletal manifestations, mostly arthralgias and myalgias, are present in up to 60% of AAV patients at diagnosis. As in our patient, such manifestations may be the first and main clinical features of the disease, until more classical ones develop. Most suggestive characteristics of GPA include ear, nose, and throat (ENT) signs (crusting rhinitis, destructive sinusitis, saddle-nose deformity) and lung nodules (with or without cavitations). Asthma and nasal (allergic) polypsis are some hallmarks of EGPA. Pauci-immune glomerulonephritis and alveolar hemorrhage are possible in all three AAV diseases, although rare in EGPA. Mononeuritis multiplex is also common to the three diseases, although it occurs more often in EGPA.

Although more than 90% of the patients with systemic GPA are anti-PR3 cANCA-positive, a few are negative. Some are positive for the other main ANCA type, anti-myeloperoxidase ANCA, which is associated more commonly with MPA. In the absence of any ENT or lung involvement typical of GPA, whether our patient has GPA or MPA is difficult to determine. Iritis is rare in each AAV and not specific to any of them. The "wisest" diagnosis to retain at this time would therefore be anti-PR3 cANCA-positive AAV. Of note, several recent clinical and genetic

studies suggested that the ANCA type could indeed have more impact on the disease course and outcomes than the distinction between GPA or MPA, which can sometimes be difficult to establish. The recently revised Chapel Hill nomenclature states that for now we should continue to describe AAV as three diseases (*i.e.*, GPA, MPA, and EGPA), rather than individualizing new vasculitis entities based on ANCA status and type. However, the nomenclature also specified that one should always add a prefix before GPA, MPA, or EGPA indicating ANCA reactivity. In our patient, the diagnosis would remain as anti-PR3 cANCA-positive "GPA or MPA".

Treatment Discussion

AAV patients show substantially higher mortality than the age-matched general population, especially if the diagnosis, the treatment, or both are delayed. Combined cyclophosphamide (CTX) and glucocorticoids have led to marked improvement in early outcomes over the past four decades; more than 90% of patients now achieve remission, compared with an 80% one-year mortality rate in the early 1950s. As was established by several subsequent studies (Table 1), conventional AAV treatment is now well codified and adjusted according to the disease severity and extent of organ involvement, to optimize the chance of remission and limit the risk of treatment-related side effects.

AAV can be separated into major-organ- or severe life-threatening disease, and into more limited forms.² Patients such as our case, who present with major organ-threatening disease (renal involvement), should be promptly treated with high-dose glucocorticoids combined with a potent immunosuppressive agent, namely CTX or rituximab. The first goal of treatment is to achieve remission, defined in our patient as the return to normal renal function or at least some recovery, then its stabilization, along with the resolution of all extra-renal manifestations. A more limited treatment strategy, such as MTX with glucocorticoids, should only be tried in patients with limited, non-severe, and non-renal disease.²

Most of the glucocorticoid regimens include initial intravenous pulses of methylprednisolone (0.5 g/d-1 g/d for one to three consecutive days) for patients with severe disease manifestations, followed by oral prednisone at 1 mg/kg/d for two to four weeks, gradually tapered by approximately 10% until reaching 10 mg/d-20 mg/d by Week 12. The subsequent tapering scheme and optimal

duration of glucocorticoid therapy remain debated, and the latter varies between six months to several years. In most of the previous European trials, the minimal duration of glucocorticoid therapy was about 18 to 24 months.

Combined with glucocorticoids, CTX has become the standard of care to induce remission in patients with severe AAV. It can be given daily and orally (2 mg/kg/d), or by intravenous pulses (15 mg/kg every two weeks for the first three pulses, then every three weeks), with dose adjustments for age and renal function. Both are equally effective, with no difference in time to remission but perhaps fewer episodes of leucopenia with the intravenous pulse regimen. Because of the toxicity (particularly the risks of infertility and delayed bladder cancer) associated with prolonged administration of CTX, this agent, when effective, must be stopped after a maximum of six months and replaced by a less toxic maintenance agent, such as azathioprine (AZA) or MTX.³ CTX can indeed be stopped once remission has been achieved (*i.e.*, often at three months);⁴ however, recent long-term follow-up of patients enrolled in some European studies showed that oral CTX was likely associated with a lower relapse rate at three years,⁵ which indeed reflects that a high cumulative CTX dose is also associated with low relapse rate (six intravenous pulses over three months leads to a total of 5 g-8 g vs. 9 g-18 g for three months of oral daily CTX). The balance between CTX efficacy and toxicity thus remains subtle and clearly applies beyond the simple induction phase.

Rituximab was recently approved by the US Food and Drug Administration, then Health Canada, based on the results of two randomized controlled trials,^{6,7} as an alternative to CTX for remission induction in adult patients with severe ANCA-positive GPA or MPA. Precise criteria for coverage of the drug may differ slightly by province. The RAVE trial⁶ compared remission induction with glucocorticoids (aiming at a total duration of six months) and rituximab (375 mg/m² per week for four weeks), then placebo AZA up to Month 18, or oral CTX (2 mg/kg/d, followed by AZA, once remission has been achieved, at 2 mg/kg/d up to Month 18) in 197 patients with GPA or MPA.⁶ Results showed the non-inferiority of rituximab compared to the conventional staged CTX-AZA approach at Month 6, which was sustained until Month 18. Rituximab is not associated with infertility or risk of late bladder cancer; however, the study showed that the risk of infections, mainly of the respiratory tract, was “disappointingly” similar with both treatment strategies.

The randomized controlled MEPEX study⁸ showed that plasma exchange (seven sessions over 14 days) was associated with more frequent renal function recovery at one year, as compared with intravenous pulses of methylprednisolone (1 g/d for three consecutive days). However, it failed to show any significant benefit in patients with pulmonary-renal syndrome in terms of survival, and the proportion of patients with end-stage renal disease beyond the first year of follow-up was eventually comparable. Because intravenous methylprednisolone pulses are indeed part of the conventional therapy for patients with severe disease, rather than an alternative to plasma exchange, and the MEPEX sample size was small, the real potential benefit of plasma exchange for severe AAV remains uncertain. The ongoing PEXIVAS trial specifically aims to determine whether plasma exchange is effective in reducing death and progression to end-stage renal disease. Several Canadian centers are participating in this international study, and every patient with AAV and renal disease (glomerular filtration rate < 50 mL/min) and/or alveolar hemorrhage should be considered and screened for eligibility.⁹

Back to Our Patient

Our patient was deemed to have anti-PR3-ANCA-positive vasculitis with severe manifestations, based on renal involvement, along with arthritis, mononeuritis multiplex, and possible iritis. He was immediately started on high-dose glucocorticoids (intravenous methylprednisolone pulses, then oral prednisone). He declined enrolment in the PEXIVAS trial and did not want plasma exchange. He was concerned about possible infertility issues with use of CTX and was offered sperm cryopreservation before starting oral CTX (2 mg/kg/d, or 150 mg/d in his case). He had no private drug plan for financial support for rituximab coverage and only had a soon-to-end student health insurance plan. He completed all the administrative paperwork needed to apply for rituximab coverage through the provincial exceptional access program and was approved after four weeks of oral CTX treatment. He then switched to rituximab. At the time of the switch, serum creatinine level was already at 140 µmol/L.

Two months after the initiation of the induction treatment, the creatinine level was 110 µmol/L, with persistent proteinuria at 1 g/L and microscopic hematuria but normal CRP level, complete motor recovery and resolving sensory peripheral neuropathy. The patient no longer has any

joint pain and has gained 10 kg. The maintenance strategy will soon have to be considered, as the patient is gradually entering remission. We could opt to treat with a repeat rituximab induction regimen only in case of disease flare/relapse, or give a conventional maintenance agent such as daily oral AZA (starting four to six months after the last rituximab infusion). Rituximab is not approved for maintenance therapy, although several retrospective studies and the French randomized controlled MAINRITSAN trial recently showed that systematic rituximab re-infusions (500 mg-2,000 mg, depending on the study, every six months) were likely more effective than AZA for maintaining remission, with a good safety profile.¹⁰

Conclusion

Although characteristic AAV target organs include the kidneys, lungs, skin, and peripheral nerves, many patients initially present with non-specific musculoskeletal symptoms and may therefore encounter some diagnostic delay. Prompt diagnosis and appropriate treatment can improve the overall outcomes. Therefore, the possibility of such rare conditions as AAV should be suggested early when a patient with arthritis presents some systemic manifestations. Close clinical and biological monitoring within the first weeks after arthritis onset is mandatory, as is usual in our general rheumatology practice. ANCA testing should be considered early in patients in whom a definite diagnosis, such as an infection or crystal arthritis, cannot be firmly established.

Over the past decades, several randomized controlled trials of AAV have led to more effective treatment strategies and safer options for AAV patients. CTX and glucocorticoids remain the cornerstone agents for inducing remission in patients with generalized and severe AAV. Rituximab has been found an effective alternative to CTX to induce remission in patients with contraindication(s) or intolerance to CTX, including those already exposed to CTX (*i.e.*, relapsers) and/or young patients in their reproductive years. Many questions still must be answered to further optimize therapeutic strategies, including the role of plasma exchange, the optimal duration of glucocorticoid and immunosuppressant treatments, and the best maintenance options after rituximab-based induction treatment. Several ongoing trials are trying to tackle these questions. Therefore, contacting and perhaps referring AAV patients to a referral center for

vasculitis, such as one of those participating in the Canadian Vasculitis (CanVasc) research network (www.canvasc.ca) should always be considered.

References

1. Anderson K, Klassen J, Stewart SA, et al. Does geographic location affect incidence of ANCA-associated renal vasculitis in northern Saskatchewan, Canada? *Rheumatology (Oxford)* 2013; 52(10):1840-4.
2. Schönemmarck U, Gross WL, de Groot K. Treatment of ANCA-associated vasculitis. *Nat Rev Nephrol* 2014; 10(1):25-36.
3. Pagnoux C, Mahr A, Hamidou MA, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med* 2008; 359(26):2790-803.
4. Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibody. *N Engl J Med* 2003; 349(1):36-44.
5. Harper L, Morgan MD, Walsh M, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis* 2012; 71(6):955-60.
6. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; 363(3):221-32.
7. Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide for ANCA-associated renal vasculitis. *N Engl J Med* 2010; 363(3):211-20.
8. Jayne DR, Gaskin G, Rasmussen N, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 2007; 18(7):2180-8.
9. University of Birmingham. Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis: an international randomised controlled trial. Available from: www.birmingham.ac.uk/research/activity/mds/trials/bctul/trials/renal/pexivas/index.aspx
10. Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *ACR Annual Meeting Abstracts. Arthritis Rheum* 2012; 64 (Suppl):1652.

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Table 1

Summary of Main Randomized Controlled Trials of ANCA-associated Vasculitis Over the Past Three Decades Which Led to Changes in the Way Patients With These Rare and Potentially Life-threatening Conditions Are Treated*

Study Name	Patients	Inclusion Criteria	Studied Intervention	Primary Endpoints	Main Findings
CYCLOPS (De Groot et al, 2009)	149	Newly-diagnosed GPA, MPA with renal disease (creatinine 150 mol/L-500 mol/L)	Pulse (mainly IV) CTX (15 mg/kg) vs. oral CTX (2 mg/kg) until remission + (in both arms) prednisolone and three-month consolidation of CTX after remission, then AZA until Month 18.	Time to remission	Pulse (IV) CTX induces remission as well as daily oral CTX, at a reduced cumulative CTX dose (8.6 g vs. 18 g) and caused fewer leucopenia. At longer term (4.3-year follow-up), no difference in survival but the rate relapse was lower in the daily oral than IV group (HR 0.50, 95% CI 0.26-0.93; $p = 0.029$).
RAVE ⁶ (Stone et al, 2010)	197	New or relapsing ANCA+, severe GPA or MPA (but creatinine < 354 mol/L and not life-threatening)	Rituximab (375 mg/m ² weekly x 4) vs. oral CTX then AZA + (in both arms) glucocorticoids (aiming to stop at Month 6)	Complete remission off glucocorticoids at six months	Rituximab is not inferior to CTX-AZA strategy at Month 6 and 18, and is superior to CTX-AZA for relapsing patients (at Month 6; only not inferior at Month 18). Similar infection rates in both arms.
RITUXVAS ⁷ (Jones et al, 2010)	44 (3:1 ratio)	Newly-diagnosed ANCA+ GPA, MPA, or kidney-limited AAV with renal disease	Rituximab (375 mg/m ² weekly x 4) + 2 IV pulses of CTX (15 mg/kg at Day 1 and Day 14) vs. IV CTX pulses only (15 mg/kg) for three to six months, then (in both arms) AZA + glucocorticoids	Sustained remission and rates of severe adverse events at 12 months	Rituximab is not superior to CTX-AZA strategy. Sustained-remission rates were high in both groups. Similar rates of early severe adverse events in both groups.
MEPEX ⁸ (Jayne et al, 2007)	137	Newly-diagnosed GPA or MPA with renal disease and creatinine > 500 µmol/L	Plasma exchange vs. methylprednisolone pulses (IV 1 g for three days) + (in both arms) oral prednisolone and oral CTX for six months, then AZA	Renal recovery at three months (dialysis independence)	A 24% reduction in risk of progression to ESRD at 12 months with plasma exchange. Longer term (4 year) HR for plasma exchange compared to IV methylprednisolone for death or ESRD of 0.81 (95% CI 0.53-1.23) with a subHR for ESRD of 0.64 (95% CI 0.40-1.05).
NORAM (De Groot et al, 2005)	100	Newly diagnosed GPA or MPA, with creatinine level <150 µmol/L and no major organ involvement	MTX (15 mg gradually increased to 25 mg/week) vs. daily oral CTX + (in both arms) oral prednisolone. All treatments stopped at Month 12.	Remission at Month 6	The remission rate was not inferior with MTX, but remission was delayed in patients with more extensive or pulmonary disease. Relapse rate at 18 months was higher in the MTX group. Adverse events were less frequent with MTX, except for liver dysfunction.
CYCAZAREM ⁴ (Jayne et al, 2003)	144	Newly-diagnosed GPA, MPA, or renal-limited disease, with at least one major organ involved (but creatinine level < 500 µmol/L)	Oral AZA (2 mg/kg) vs. continuation of oral CTX (1.5 mg/kg) for 12 months (then AZA for all until month 18) + all induced with oral CTX and prednisolone until remission (three to six months) then randomized for maintenance	Relapse (major or minor) and adverse events at Month 18	No difference in relapse and adverse event rates between groups (results of longer term follow-up are under analysis).
WEGENT ³ (Pagnoux et al, 2008)	126	Newly-diagnosed systemic GPA or MPA	MTX (0.3 mg/kg/week, oral or subcutaneous) vs. oral AZA (2 mg/kg/d) for 12-16 months + all induced with IV CTX pulses and prednisone until remission (three to six months) then three consolidation pulses before randomization for maintenance	Adverse events (severe and/or leading to study drug cessation) and relapse	No difference in relapse and adverse event rates between groups (results of longer term follow-up are under analysis).
IMPROVE (Hiemstra et al, 2010)	165	New or relapsing ANCA+, severe GPA or MPA (but creatinine < 354 mol/L and not life-threatening)	Oral MMF (2 g/d) vs. oral AZA (2 mg/kg/d) until Month 42 + all induced with IV or oral CTX pulses and prednisolone until remission (three to six months) then randomization for maintenance	Relapse-free survival and adverse events	MMF was less effective than AZA for maintaining disease remission (HR of relapse 1.69 (95% CI 1.06-2.70; $p = 0.03$). Severe adverse events did not differ significantly between groups.

*All studies are reviewed in more detail in the referenced review article.²

ANCA = anti-neutrophil cytoplasm antibodies; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; IV = intravenous; CTX = cyclophosphamide; AZA = azathioprine; HR = hazard ratio; AAV = ANCA-associated vasculitis; MTX = methotrexate; MMF = mycophenolate mofetil; ESRD = end-stage renal disease.