Management of rapidly progressive glomerulonephritis

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Rapidly progressive glomerulonephritis (RPGN) causes the loss of renal function in a matter of weeks or months. Early recognition is important as treatment may prevent the development of end-stage renal failure.

Causes of RPGN

The glomerular and systemic diseases which may present with RPGN are listed in Table 1. Small vessel vasculitis, usually associated with anti-neutrophil cytoplasmic antibodies (ANCA), is the most common diagnosis. Anti-glomerular basement membrane antibody-mediated nephritis (anti-GBM disease), is much rarer, but is notable as the most rapidly progressive of all.

Clinical picture and investigations

The diagnosis of RPGN should be suspected in the presence of a rapidly rising creatinine with blood and protein in the urine, and is supported by the finding of urinary red cell casts. Until significant uraemia is present, it is rare for symptoms to arise from the nephritis itself.

Characteristic clinical features may reveal the underlying diagnosis – for example the granulomas in the upper and lower respiratory tract of Wegener’s granulomatosis. However, certain illnesses may look superficially similar: microscopic polyangiitis, mixed essential cryoglobulinaemia and infectious endocarditis may all cause a febrile illness with vasculitic skin lesions and RPGN. Both vasculitis and anti-GBM disease may present with pulmonary haemorrhage and RPGN, and both may present without extrarenal disease.

Further investigations are aimed at confirming a severe glomerulonephritis, and making a specific diagnosis. Serological tests should include assays for ANCA, anti-GBM and lupus autoantibodies, and assays for cryoglobulins should be considered. Measurements of serum complement components can help distinguish between RPGN due to lupus, cryoglobulinaemia, or infection (certain components reduced) – and vasculitis-associated RPGN and anti-GBM disease (complement levels normal or increased).

These serological markers do not have 100% sensitivity and specificity, and unless the risks are unusually high, a renal biopsy should be performed and examined by light microscopy and for immune

Table 1. Causes of RPGN.

| ANCA-associated systemic vasculitis |
|-----------------------------------|
| Anti-GBM disease (Goodpasture’s disease) |
| Crescentic phase of primary glomerulonephritis |
| Post-infectious glomerulonephritis |
| Other systemic diseases |

With extrarenal vasculitis

- Wegener’s granulomatosis
- Microscopic polyangiitis
- Without extrarenal vasculitis
- Idiopathic RPGN

For example

- IgA nephropathy
- Mesangiocapillary glomerulonephritis

SLE

- Mixed essential cryoglobulinaemia
- Relapsing polychondritis
- Chronic infection
- Malignancy

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reactants by immunofluorescence or immunoperoxidase methods.

Table 2 summarises the typical clinical and laboratory findings in RPGN due to vasculitis and anti-GBM disease. The following discussion will focus on these conditions, as the remaining syndromes listed in Table 1 are individually uncommon causes of RPGN and vary in treatment and prognosis.

**Treatment**

**Induction therapy**

Conventionally, this comprises oral prednisolone and oral cyclophosphamide. Typical regimens are shown in Table 3. Cyclophosphamide should be combined with a high fluid intake (renal function permitting), to reduce the risk of bladder toxicity, and the white cell count should be monitored regularly and the drug discontinued temporarily if the white cell count falls below a threshold value (usually 4 x 10^9/l). Consideration should be given to prescribing cotrimoxazole as prophylaxis against pneumocystis, isoniazid prophylaxis against recurrent tuberculosis (in susceptible patients), amphotericin B lozenges to prevent mucosal candidiasis and H2-antagonists for peptic ulceration.

**Adjunctive therapy**

In severe vasculitis-associated RPGN, additional therapy is usually given, comprising either pulsed methylprednisolone or plasma exchange (see Table 3). Data from randomised controlled trials support the use of plasma exchange at high intensity in severe RPGN^2, but suggest that it is not beneficial if used at low frequency and volume^3 or in lesser degrees of renal failure^2^4. Additional uncontrolled series support the use of methylprednisolone^5^6 or plasma exchange^5^ in severe RPGN; a randomised European trial comparing the two therapies is in progress.

In anti-GBM disease, plasma exchange should be performed at the earliest opportunity and continued daily until antibody levels have fallen to near the normal range. This typically requires at least 14 days of treatment. Methylprednisolone is not part of conventional treatment.

**Maintenance therapy**

In vasculitis-associated RPGN it is usual for aggressive induction therapy to be followed by a less toxic maintenance regimen aimed at preventing early relapse. In the UK, this typically comprises prednisolone and azathioprine (see Table 3). Azathioprine 2–3 mg/kg/day replaces cyclophosphamide and the dose is tapered to 1–1.5 mg/kg/day within one year. Elsewhere, reducing doses of cyclophosphamide may be employed, as described by the NIH.
group for Wegener’s granulomatosis. Since continuing corticosteroids are common to most regimens, consideration should be given to measures to prevent osteoporosis (including calcium supplementation) and to monitoring of bone density.

In anti-GBM disease, maintenance therapy is not required, and treatment is tailed off after two to three months, provided the antibody level is reduced to the background level for the assay.

Alternative regimens

There is growing enthusiasm for the administration of cyclophosphamide as intravenous pulses, to reduce the total dose and to allow co-administration of mesna to protect the bladder. Results to date (using doses varying from 375 mg/m² to 1 g/m² per pulse, at intervals of three or four weeks) have been mixed, where renal disease is prominent, it appears to induce remission of vasculitis as effectively as oral administration, with fewer infective complications. However, early relapses may be more frequent. The rate of recovery from dialysis dependence may be lower but the number of dialysis-dependent patients reported so far is small.

Occasionally, remission is not achieved with conventional drug combinations. Plasma exchange or pulsed methylprednisolone may then be added, or newer treatments considered, ideally at specialist centres with some experience of their use. These include courses of intravenous immunoglobulin, and anti-T lymphocyte antibodies. Cyclosporin has been used in selected cases with benefit. Methotrexate may be useful for non-renal vasculitis, but its toxicity in the presence of renal impairment limits its application to RPGN.

Timing and urgency of intervention

If the clinical diagnosis is uncertain, investigation is urgent. However, if the clinical diagnosis of RPGN seems secure and an infectious cause is unlikely, treatment should be commenced without delay while awaiting full investigation. It is best to avoid performing renal biopsy on the same day as plasma exchange, because the clotting factor depletion increases the risk of bleeding. A clinical decision must be made as to whether the benefits of an early diagnosis outweigh the increased risk incurred by the biopsy.

Prognosis

Survival

Overall patient survival in ANCA-positive RPGN is 70–80% at one year and 50%–70% at five years. Early deaths are usually due to pulmonary haemorrhage or opportunist infection. In the reported series of patients with anti-GBM disease, survival has been variable; the main determinant is the presence or absence of pulmonary haemorrhage.

Renal recovery

Improvement in renal function occurs in most patients with vasculitis-associated RPGN, and 60–80% of dialysis-dependent patients recover renal function. In our experience, this improvement is maintained long-term for the majority of patients. Exceptions are patients with significant residual renal impairment after the initial episode and those with a further episode of nephritis. Renal recovery from dialysis-dependent renal failure is rare in anti-GBM disease. It may be appropriate to avoid, or curtail, immuno-suppressive therapy in anuric patients with proven, typical, anti-GBM disease without pulmonary haemorrhage. This does not apply to the minority of patients with coexisting ANCA whose response to therapy may be similar to that of vasculitis-associated RPGN.

Morbidity

The treatments used in RPGN have significant side-effects, summarised in Table 4. When similar, although more prolonged, regimens were used with variable renal involvement at the NIH in Wegener’s granulomatosis, drug toxicity affected over half the patients. The long-term risks of cyclophosphamide can be reduced by keeping the course of treatment short.

Many patients are also left with significant residual organ damage from extrarenal vasculitis.

Relapse

Relapse is a major problem after vasculitis-associated RPGN, occurring in up to 50% of vasculitis patients under long-term follow-up. It may or may not affect the kidney, and does not always reproduce the presenting illness. Vasculitis may relapse after some years in remission and relapses can occur in both dialysis-dependent and transplanted patients. Relapse is exceptional in anti-GBM disease.

Strategies to reduce the risk of relapse in ANCA-associated vasculitis include the use of long-term low dose

Table 4. Adverse effects of therapy.

| Corticosteroids | infection | osteoporosis |
| Cyclophosphamide | bone marrow toxicity | avascular necrosis |
| Plasma exchange | bleeding, allergy to plasma products | changes in mood and appearance |

Corticosteroids

peptic ulceration

cataracts
diabetes

Bone marrow toxicity

Azoospermia and ovarian failure

Haemorrhagic cystitis and bladder carcinoma

Increased risk of malignancy

Methotrexate

Cyclophosphamide

Plasma exchange
maintenance immunosuppression17, continuous cotrimoxazole (in Wegener’s granulomatosis, where the predominant effect is to reduce upper respiratory tract relapses)18, and tailoring of therapy according to ANCA levels. Raised ANCA titres are generally detectable during active disease, and rising concentrations may herald relapse19-21; persisting ANCA are associated with a high risk of relapse. Few clinicians would institute treatment on the basis of a rising ANCA titre alone, although this has been suggested22, but it may be prudent to continue maintenance immunosuppression in patients who remain ANCA positive.

Prognostic factors

In vasculitis-associated RPGN, pulmonary haemorrhage and dialysis-dependent renal failure at presentation are associated with a higher mortality23. In some series older patients have had a poorer outcome24. Renal prognosis is poorer if renal failure is severe at presentation, particularly in anti-GBM disease. Early diagnosis is therefore important, and increased awareness of RPGN as a condition which needs prompt treatment should improve the outlook25.

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