From microscopic haematuria to kidney failure: The hidden progression of IgA nephropathy

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Background
Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis and a leading cause of chronic kidney disease globally. IgAN often presents with varied symptoms, and general practitioners (GPs) play a key role in its early detection and management.

Objective
This review aims to provide GPs with an overview of IgAN, focusing on clinical presentations that warrant referral to nephrology and highlighting common pitfalls in primary care management with a case example.

Discussion
Recognising high-risk features of IgAN through symptoms such as haematuria or proteinuria, addressing modifiable factors and understanding recent advances in management are vital for improving patient outcomes. New therapies targeting pathogenic pathways underscore the importance of collaborative care.

IMMUNOGLOBULIN A NEPHROPATHY (IgAN) is a major contributor to chronic kidney disease (CKD) worldwide, affecting an estimated 200,000–350,000 individuals annually.[1] Approximately one-third of patients with IgAN develop kidney failure within 20 years of diagnosis, highlighting its significant clinical burden.[1] Traditionally managed by nephrologists, the early manifestations of IgAN often present in primary care settings. This article aims to outline the clinical features, management strategies and recent therapeutic advances in IgAN, offering guidance for general practitioners (GPs) in improving patient outcomes through early intervention.

CASE PRESENTATION

A man of Asian descent, aged 51 years, with long-standing painless microscopic haematuria, was found to have a papillary urothelial neoplasm of low malignant potential on surveillance cystoscopies. He was referred to nephrology because of a decrease in estimated glomerular filtration rate (eGFR) from 72 to 59 mL/min/1.73 m^2 on his last round of blood tests 12 years prior. During the consultation, he was found to be hypertensive at 150/90 mmHg, and further urinalysis revealed an elevated urine albumin–creatinine ratio (uACR) of 71.8 mg/mmol, with no previous values for comparison. These findings, in the context of haematuria and hypertension, raised suspicion for glomerulonephritis, prompting a kidney biopsy. The biopsy confirmed IgA nephropathy, showing chronic vascular changes and 15 out of 29 glomeruli sclerosed, indicating significant chronic kidney damage. He was promptly started on an angiotensin receptor blocker and a sodium-glucose cotransporter-2 (SGLT-2) inhibitor.

Clinical presentation

IgAN is a multifaceted condition that arises from the interplay of genetic susceptibility, environmental factors and immune dysregulation.[2,3] A simplified model of this process is shown in Figure 1. IgAN presents with a wide range of clinical manifestations, making its diagnosis and management challenging. It can range from asymptomatic microscopic haematuria to more severe forms, such as nephrotic syndrome or rapidly progressive glomerulonephritis.[4] A common trigger for symptoms is an upper respiratory or gastrointestinal infection, which leads to the phenomenon known as synpharyngitic haematuria, where patients present with haematuria following an episode of an upper respiratory tract infection, typically involving the throat or pharynx.[4]

For some individuals, the first sign of IgAN is detected through screening for hypertension, where asymptomatic microscopic haematuria or proteinuria might be found. Key clinical features that should raise suspicion for IgAN

as well as other types of glomerulonephritis include any combination of haematuria, hypertension, declining kidney function or persistent proteinuria, with or without oedema. When these features are present, there is an increased risk of progression to advanced chronic kidney disease and a referral to a nephrology service is warranted, and this referral should be urgent if there are features of acute nephritis, such as rapid onset of oedema, severe hypertension, gross haematuria or rapid decline in kidney function.

As the case above reinforces, any presentation with haematuria should be further investigated and an initial uACR should be checked. An algorithm for investigating haematuria can be found in Figure 2. Delays in referral can lead to missed opportunities for early intervention, particularly in cases where disease progression is subtle but ongoing. In contrast, an early diagnosis and nephrology referral can significantly improve outcomes for patients. For further guidance, the Kidney Health Australia 'Chronic Kidney Disease (CKD) Management in Primary Care'[5] handbook offers a valuable, evidence-based resource for the detection, assessment, management and referral of glomerulonephritis and CKD, ensuring optimal care and timely specialist intervention.

Hypertension and declining kidney function are often indicators of chronic kidney damage, prompting further investigation, such as urinalysis. However, delayed diagnosis can occur when haematuria is attributed to benign conditions (eg urinary tract infections) or urological malignancies, and failure to screen for proteinuria.

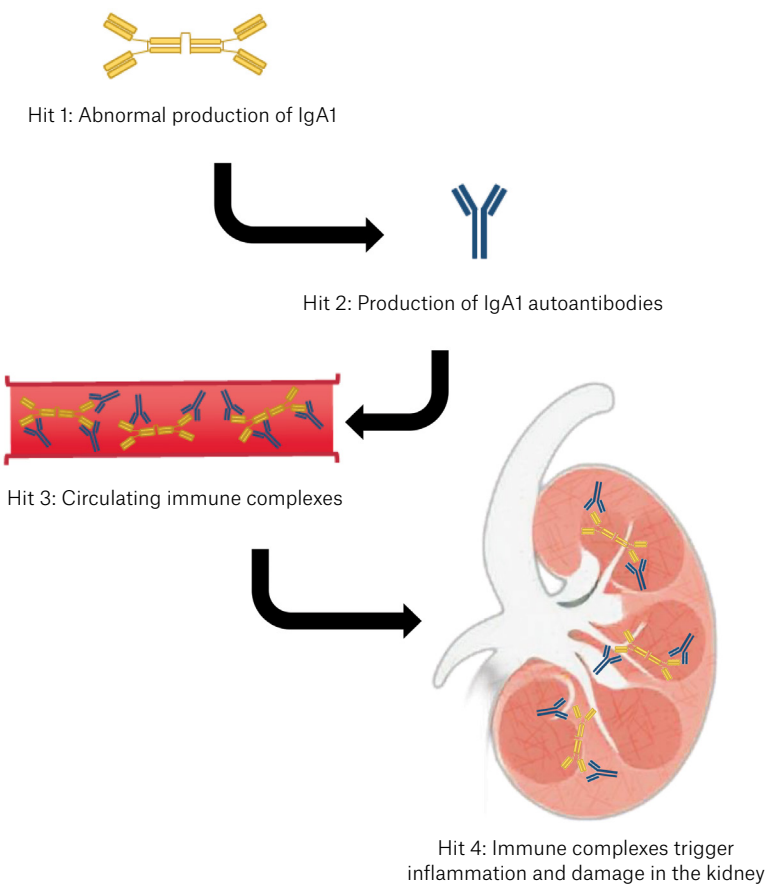

Figure 1. Simplified four-hit model of immunoglobulin (Ig)A nephropathy pathogenesis.

Ultimately, confirming the diagnosis of IgAN requires histological evidence, typically obtained through a kidney biopsy, which reveals mesangial IgA deposits on immunofluorescence microscopy. This confirms the diagnosis and allows for appropriate treatment strategies to be implemented, potentially slowing disease progression.

Prognosis and risk factors for progression

A number of traditional risk factors are associated with the progression of IgAN to kidney failure. Previously established cohort studies have found a number of traditional risk factors for progression, including higher levels of proteinuria at presentation, hypertension and reduced renal function at diagnosis (defined as creatinine clearance <75 mL/min).[6] It is crucial to recognise that kidney survival rates can vary widely among patients with IgAN. In reviewing the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry, the 44th annual report notes that diabetic kidney disease remains the most common cause of new patients presenting with kidney failure (defined as when kidneys have stopped working so treatment such as dialysis or a transplant is needed to sustain life) at 38% compared with IgAN at 5%.[7] However, IgAN remains the leading cause of primary glomerulonephritis resulting in kidney failure, accounting for 30% of primary glomerulonephritis cases that led to kidney failure in Australia in 2020.[7] IgAN is more common and severe in individuals of Asian descent.[8]

The largest recent study on IgAN prognosis, conducted by Pitcher et al,[9] analysed data from 2299 adults and 140 children enrolled in the Rare Kidney Disease Registry. Over a median follow-up of 5.9 years, the study found that 50% of patients reached kidney failure or died during the study, with a median kidney survival of 11.4 years. Notably, although higher time-averaged proteinuria was linked to worse kidney survival, even patients traditionally considered low risk (proteinuria <1 g/day) had significant rates of kidney failure within 10 years. However, this registry study only enrolled patients

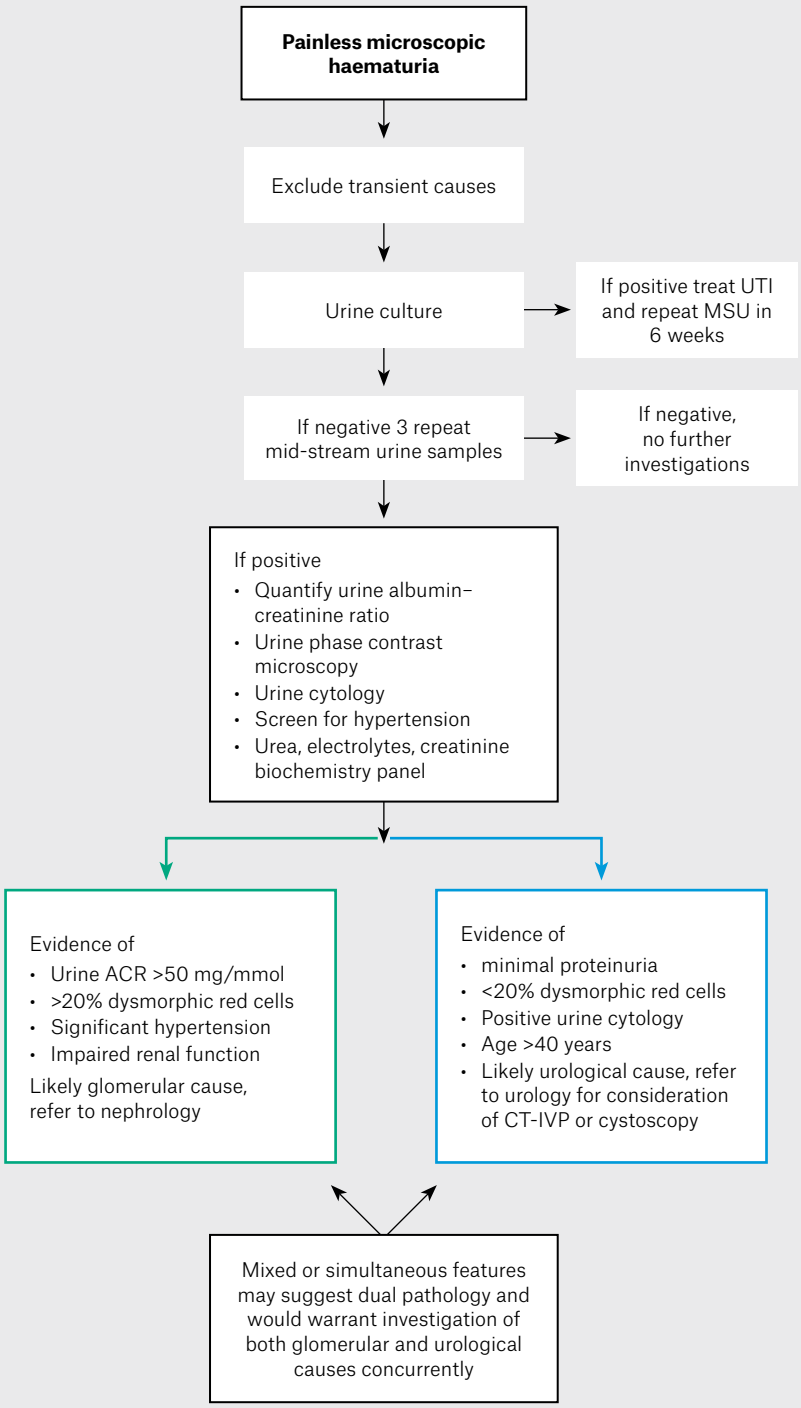

Figure 2. Painless microscopic haematuria investigation algorithm.

ACR, albumin–creatinine ratio; CT-IVP, computed tomography–intravenous pyelogram; MSU, midstream urine; UTI, urinary tract infection.

with proteinuria >0.5 g/day and/or an eGFR <60 mL/min/1.73 m^2. This underscores the importance of not underestimating the risk in patients with lower levels of proteinuria.

Although mild cases of IgAN might have a relatively favourable long-term prognosis without treatment, all patients with IgAN should be regularly monitored by a nephrologist. Even in the absence of overt proteinuria or symptoms, disease progression can still occur, particularly in those with pre-existing CKD. Regular assessment of eGFR, proteinuria and blood pressure, coupled with adherence to lifestyle and pharmacological interventions, forms the backbone of ongoing care in the primary care setting.

Management of IgAN

The management of IgAN centres on delaying disease progression through optimal supportive care while addressing high-risk features such as proteinuria, hypertension and declining kidney function. Best supportive care, as recommended by Kidney Disease: Improving Global Outcomes (KDIGO) guidelines,[10] forms the cornerstone of therapy. This approach includes lifestyle modifications such as dietary sodium reduction, smoking cessation, weight management and regular exercise. Blood pressure control to a target of 120–130/70 mmHg and the use of renin–angiotensin–aldosterone system (RAAS) inhibitors are particularly critical in reducing proteinuria and preserving renal function.[10] RAAS blockade at a maximum tolerated dose is advised for all patients with proteinuria >0.5 g/day regardless of hypertension.

The advent of SGLT-2 inhibitors has expanded the treatment options for IgAN. Trials such as DAPA-CKD[11] and EMPA-KIDNEY[12] demonstrated substantial benefits in slowing kidney disease progression among patients with non-diabetic CKD, including IgAN. Dapaglifozin and Empagliflozin are now readily available on the Pharmaceutical Benefits Scheme by authority prescription for chronic kidney disease of eGFR 25–75 mL/min/1.73 m^2 and uACR 22.6–565 mg/mmol if otherwise stabilised on RAAS blockade for at least four weeks.[13,14]

Although immunosuppression remains a cornerstone for high-risk patients, particularly those with persistent proteinuria despite optimal supportive care, its use is tempered by concerns over treatment-emergent toxicity. Corticosteroids, long utilised for their immunomodulatory effects, reduce proteinuria and delay progression but are associated with significant adverse events, including severe infections.[3,15]

Recent advancements in targeted therapies have opened up a range of treatment options in a previously sparse field. These emerging therapies have sought to mitigate the risks associated with conventional immunosuppression. Budesonide, in its intestine-targeted delayed-release form, has shown promise in reducing proteinuria by targeting mucosal B lymphocytes while minimising systemic side effects.[16] Novel agents such as Sibeprenlimab, a monoclonal antibody targeting A Proliferation-Inducing Ligand (APRIL),[17] dual APRIL/B-Cell Activating Factor (BAFF) and inhibitors like Atacicept[18] offer a targeted approach by reducing IgA production and immune complex formation. Complement inhibitors, including Iptacopan[19] and other agents targeting the alternative and terminal complement pathways, are under active investigation and have shown encouraging results in preliminary studies.

A general primary care management guideline for IgAN can be found in Figure 3.

Conclusion

IgAN exemplifies the complex interplay of genetic, immunologic and environmental factors in CKD. Although traditional management strategies have focused on supportive care and limited immunosuppression, the advent of targeted therapies offers new hope for improved outcomes. Early detection and recognition of clinical presentations such as persistent haematuria and proteinuria is vital for timely referral and optimised patient care.

Key points

- IgAN is a major cause of CKD, with one-third of patients developing kidney failure within 20 years.
- Early manifestations such as microscopic haematuria and hypertension often present in primary care and require prompt investigation.
- Key risk factors for progression include proteinuria, hypertension and reduced eGFR, necessitating long-term monitoring.
- Management focuses on supportive care, blood pressure control and RAAS inhibitors, with SGLT-2 inhibitors expanding treatment options.

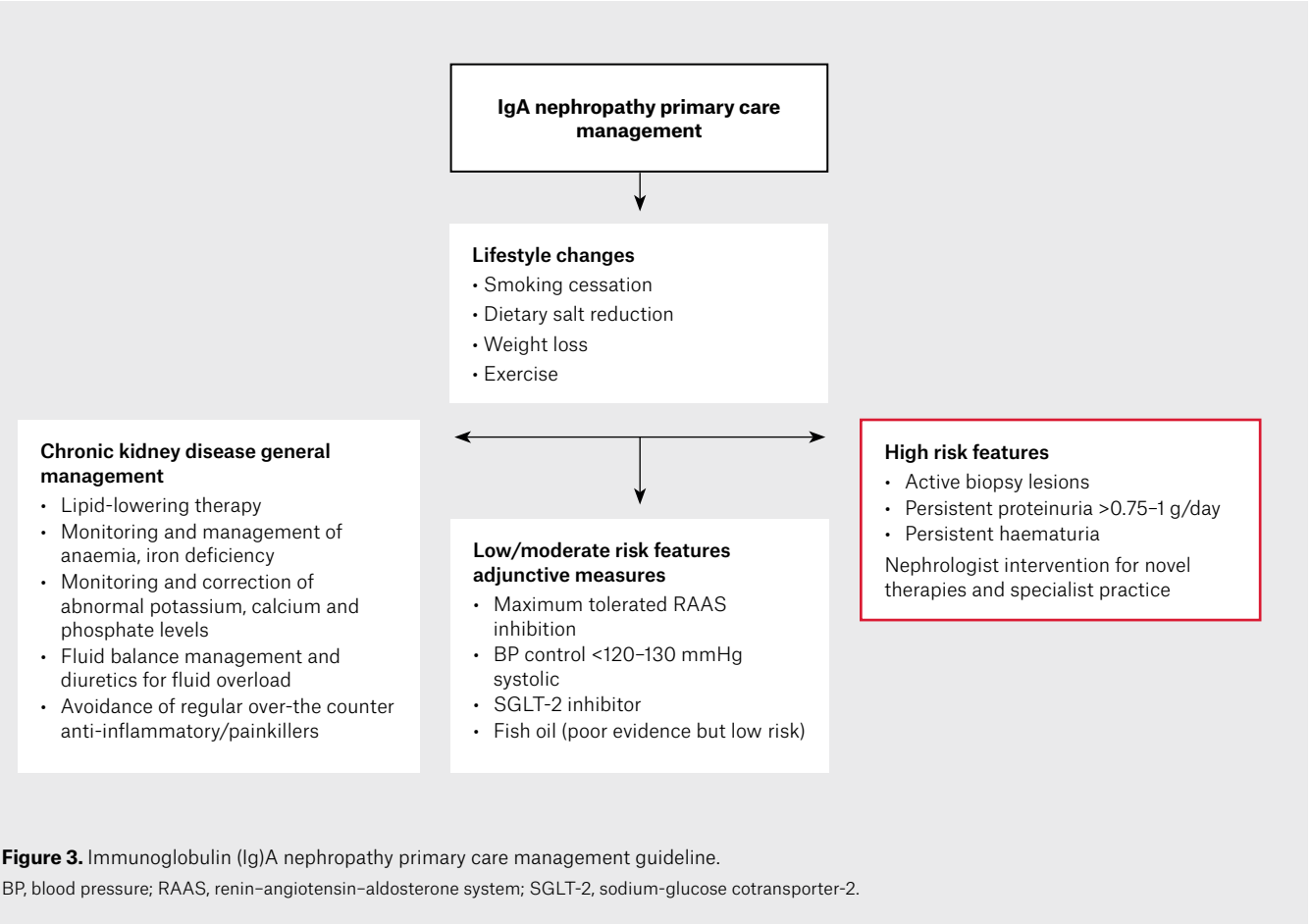

Figure 3. Immunoglobulin (Ig)A nephropathy primary care management guideline.
BP, blood pressure; RAAS, renin–angiotensin–aldosterone system; SGLT-2, sodium-glucose cotransporter-2.

- Emerging therapies, including targeted immunomodulation and complement inhibitors, offer potential for improved outcomes.

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