CASE REPORT

The eyes that saw the kidneys

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SUMMARY

Renal involvement in sarcoidosis is very uncommon and often diagnosed through renal biopsy. It is a chronic and multisystem disease with unknown aetiology and can affect all organs of the body with strong predilection to the lungs. Although glucocorticoids are effective in the treatment of sarcoidosis, the mainstay of management includes supportive hydration and prevention of nephrotoxins. We report a case of a young man who was admitted with an ocular and renal impairment secondary to sarcoidosis.

INTRODUCTION

Sarcoidosis is a rare multisystem disease caused by noncaseating granulomas with highly variable course. Its aetiology remained unknown and renal involvement is uncommon. We present a case of a 32-year-old male patient admitted with ocular symptoms and renal impairment secondary to sarcoidosis.

CASE REPORT

A 32-year-old Indian man was referred to the Ophthalmology clinic for eye assessment with a complaint of incidental finding of left eye small whitish spots. There was no history of recent eye redness, photophobia, blurring of vision, floaters, or trauma. On examination, his visual acuity was 6/9 with glasses bilaterally. Anterior segment examination showed old mutton-fat pigmented keratic precipitates with anterior chamber cells of 1+ and presence of pigmented anterior vitreous cells of 1+ bilaterally. Fundus examination revealed bilateral hyperaemic discs and periphlebitis around the optic disc with candle wax dripping appearance. There was one focal small choroiditis seen at the peripheral fundus of right eye superiorly. Optical coherence tomography revealed no evidence of cystoid macular oedema. Unfortunately, he had not consented for fundus flurescein angiography for further evaluation.

Further questioning revealed that he had history of frothy urine three months prior to presentation. His blood investigations in Ophthalmology clinic showed normal range of complete blood count, liver function test, erythrocyte sedimentation rate, and C-reactive protein. His Mantoux test result was 0 mm. He was started on topical corticosteroids by the Ophthalmologist in view of good visual acuity with no macula oedema. Renal profile however showed raised serum creatinine 156 µmol/L, and he was referred to the Nephrology clinic for further evaluation.

On review in Nephrology clinic, he denied any constitutional symptoms of weight loss, night sweats, altered bowel habit, joint pain, alopecia, and oral ulcerations. He denied taking any regular medications or supplements. His family history was not significant for any renal disease. He is the fourth of six siblings, and he worked as a painter. He was a non-smoker and denied indulging in any high-risk behaviour. Clinical examination was unremarkable.

Further investigation revealed that serum creatinine rose to 180 µmol/L, which later peaked at 206 µmol/L and mild hypercalcaemia (serum calcium 2.61 mmol/L). Other blood investigations were not significant: phosphate level of 0.87 mmol/L, alkaline phosphatase 68 U/L, hepatitis B, C and human immunodeficiency virus screening negative, intact parathyroid hormone not elevated, serum antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA) negative, and serum and urinary paraproteins not detected. Urinalysis revealed urine protein 1+ and blood trace, and urine protein creatinine index (PCI) was mildly elevated at 0.06 g/mmol Cr. His 24-hour urine calcium was elevated at 17.7 mmol/day (normal range 2.5–8.0 mmol/day). Ultrasound of his kidneys showed normal kidney size with no obstructive uropathy. His chest radiograph showed normal heart size with no perihilar lymphadenopathy. A baseline spimometry also showed normal lung function capacity. Serum angitensin-converting enzyme (ACE) was elevated at 124 U/L (normal range 16–85 U/L).

Renal biopsy was performed and showed granulomatous inflammation with tubulointerstitial nephritis and no morphological features of glomerulonephritis. Immunofluorescence stains were inconclusive but the Ziehl-Nelson stain was negative. A diagnosis of systemic sarcoidosis with ocular and renal involvement was made.

He was started on prednisolone at a dose of 20 mg (0.5 mg/kg/day) and later discharged with outpatient follow-up. He remained asymptomatic with no other organ involvement. However, his renal function did not normalised despite being treated with prednisolone for six months. At 16 months after initial presentation, his creatinine rose to 173 µmol/L but there was no proteinuria. It was decided for a repeat course of prednisolone, but starting dose was 1 mg/kg/day. His renal function improved within a month, and the prednisolone was tapered rapidly within two months. The latest outpatient review at 20 months after initial presentation showed a stable renal function (creatinine 121 µmol/L and urinary protein-creatinine ratio of 7 mg/mmol). His uveitis remained stable with no worsening of vision.

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Table I: Treatment Algorithm for Sarcoidosis

First line:
Glucocorticoids:
Oral prednisolone 0.5–1.0 mg/kg/day
Taper dose by 5 mg per week after 4 weeks (unless no clinical improvement)
Duration of treatment: 6–12 months
Consider IV Methylprednisolone 500–1000 mg/day for 3 days followed by oral prednisolone 1 mg/kg/day (in those with major organ involvement)
Second line:
Steroid-sparing agents:
Azathioprine 2 mg/kg/day (maximum 200 mg/day)
Methotrexate 10–20 mg/week (to be supplemented with folic acid)
Mycophenolate mofetil 1000 mg BD
*Taper glucocorticoid dose by 5 mg weekly until 5–10 mg daily
Third line:
Tumour necrosis factor – alpha inhibitor:
Infliximab 3–5 mg/kg at weeks 0, 2, 6 and every 6–8 weeks thereafter

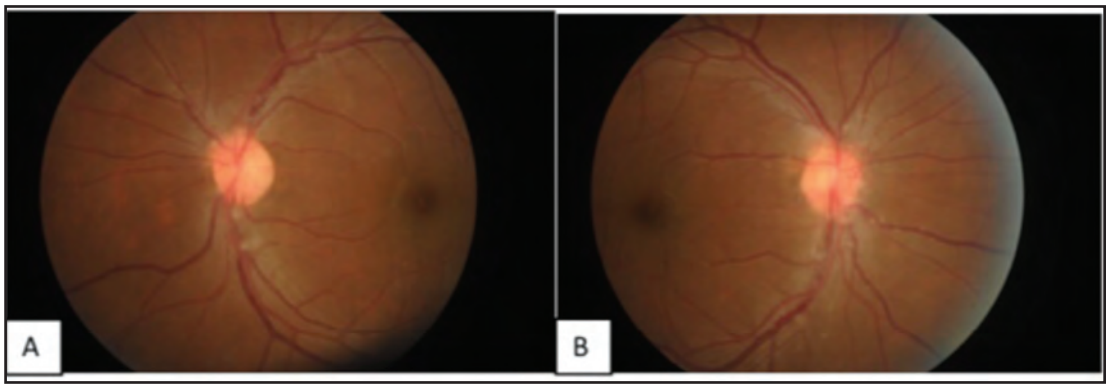

Fig. 1: Fundal image
Bilateral hyperemic optic disc with segmental area of periphlebitis in the (A) left and (B) right eye.

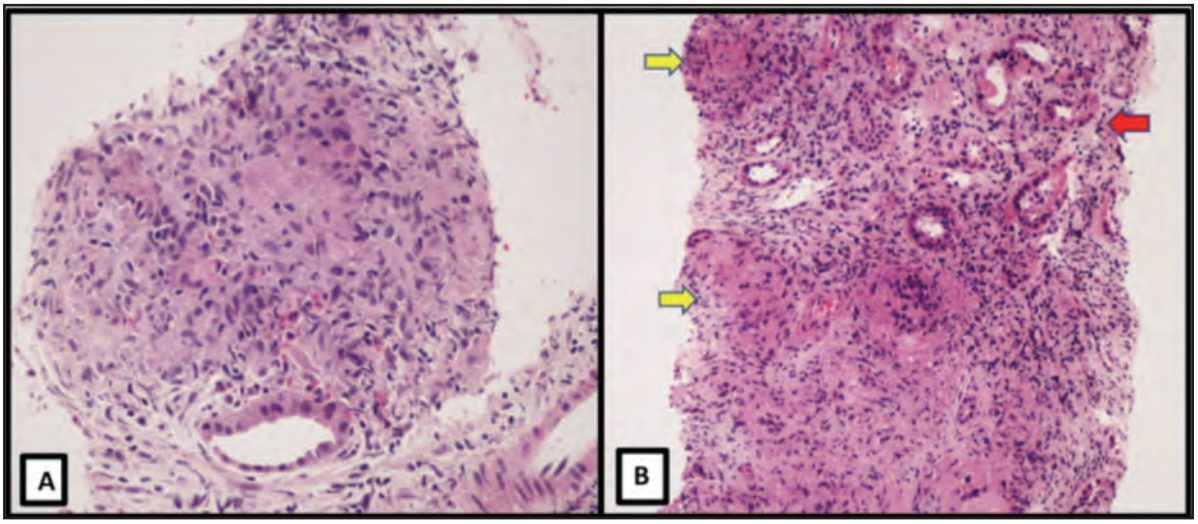

Fig. 2: Light microscopy of kidney biopsy specimen
There are numerous nodules seen in renal cortical tissue, which mainly comprised of epithelioid histiocytic granulomata (yellow arrow) in (B) with some interstitial inflammation. Renal tubules are readily seen (red arrow). In (A), the granuloma is composed of aggregates of epithelioid histiocytes admixed with multinucleated giant cells and scattered lymphocytes. No definite necrosis is seen. (A) Hematoxylin-eosin stain (H&E; original magnification, x200) and (B) H&E (original magnification, x100).

DISCUSSION

The incidence of sarcoidosis varies according to geographical regions and is affected by gender and race. It is very uncommon in Malaysia but patients of Indian race appeared to be more susceptible to sarcoidosis compared to other ethnicities.[1] Because of its heterogeneity of multiorgan involvement, many cases remained undiagnosed. It is believed that the disease is now much more prevalent with higher mortality rates than previously reported.[2] Although majority had benign self-limiting course of disease, up to a third of the patients will develop chronic disease leading to significant organ failure. Sarcoidosis appears more common in young adults.[3]

The diagnosis of sarcoidosis is not standardised and often by exclusion. Three major criteria needed to aid the diagnosis include a compatible clinical presentation, the finding of non-necrotising granulomatous inflammation on tissue biopsy, and exclusion of alternative causes of granulomatous disease.[3] Diagnosing sarcoidosis is often a challenge due to the many clinical and radiological similarities it shared with tuberculosis, a highly prevalent chronic granulomatous disease in Malaysia.[1] Sarcoidosis involving both renal and eye disease is extremely rare. We believe this is the first case reported in our country.

Renal sarcoidosis has a wide spectrum of clinical manifestations ranging from asymptomatic state to progressive and relapsing disease. The most typical form of renal sarcoidosis is the granulomatous interstitial nephritis, followed by secondary glomerulonephritis such as IgA nephropathy and membranous nephropathy. Impaired calcium homeostasis, occured as a result of abnormal vitamin D production due to over-expression of 1-alpha-hydroxylase, often lead to nephrolithiasis and nephrocalcinosis. In addition, calcium precipitates may obstruct both the proximal and distal tubules and cause acute tubular necrosis. Amyloidosis is a rare manifestation of renal sarcoidosis.[4,5]

Urinary abnormalities are not specific as seen in our case. One should remember that bland urine sample does not exclude renal involvement. Serum angiotensin-converting enzyme is also not specific to sarcoidosis as it can be elevated in other granulomatous disorders and even in end-stage kidney disease of varying causes. Nonetheless, it can still be useful as a marker of disease severity and to assess treatment response.[5]

Histopathological evaluation is often required to establish the diagnosis. A typical sarcoidosis granuloma has well-formed, concentrically arranged layer of immune cells, most prominent being the central core of macrophage aggregates and multinucleated giant cells, and often non-necrotic. Again, one should remember that absence of such renal biopsy findings does not exclude the the diagnosis as lesions can be focal and missed on biopsy.[3,5]

In 2017, the International Workshop on Ocular Sarcoidosis (IWOS) published a revised criteria for diagnosing ocular sarcoidosis. This criteria was based on seven clinical signs and eight systemic investigation results, and other causes of granulomatous uveitis must be ruled out.[6] In this case, our patient had three ocular clinical signs: mutton-fat keratic precipitates, segmental periphlebitis with candle wax dripping and bilateral involvement, and fulfilled two systemic investigation in suspected ocular sarcoidosis, which was negative tuberculin test and elevated serum ACE. In terms of ocular management, his initial treatment was topical corticosteroids as there was significant anterior chamber inflammation with no cystoid macula oedema formation. Subsequent treatment with oral corticosteroid was indicated after confirming the diagnosis of renal sarcoidosis, and his eye manifestations of hyperaemic disc and periphlebitis were resolved.[7]

Although there is no strong evidence from randomised controlled trials, management of renal sarcoidosis has been largely focussed on optimising hydration to treat hypercalcaemia and hypercalciuria as well as using corticosteroids in treating interstitial nephritis. Intravenous saline hydration is often the first initial therapy in these patients as hypercalcaemia often leads to dehydration. Concomitant loop diuretics will help enhance urinary calcium excretion. Use of thiazide diuretics should be avoided in these patients. Glucocorticoids are used to reduce calcium absorption by inhibiting the activity of 1-alpha hydroxylase. Dose and duration of treatment remain unestablished, but many recommended initiation dose of 0.5–1.0 mg/kg/day. Other preventive measures include low dietary calcium and vitamin D intake and limiting exposure to sunlight.[5]

Glucocorticoids, namely prednisolone, remain the most effective treatment for interstitial nephritis. However, other immunosuppressive drugs such as methotrexate, azathioprine, and mycophenolate mofetil are also used as steroid-sparing agents or in patients who have failure or contraindications to glucocorticoids. The evidence for these agents is limited to case series only. Tumour necrosis factor (TNF) alpha inhibitor such as infliximab has been used in several case studies in treatment of steroid-resistant sarcoidosis. TNF is thought to be responsible in granuloma formation, and therefore, its inhibition is postulated to be helpful in these resistant cases.[5] Another biologic agent of interest is adalimumab, but more data on its efficacy are required. Refer to Table I for comparison of agents.

Although majority of patients undergo disease remission, it is not uncommon that some patients progress to end-stage kidney disease. These patients are commonly elderly and have failed to respond to first-line treatment, or they have multiorgan involvement. Another poor prognostic factor is presence of kidney scarring at presentation. Morbidy from chronic sarcoidosis can also be substantial, and this is often more prominent in those with lower socioeconomic status.[8,9]

CONCLUSIONS

Sarcoidosis with renal and ocular involvement is rare. Renal biopsy, in this case, is vital to establish the diagnosis and initiate prompt treatment. Management via multidisciplinary approach is of paramount importance.

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