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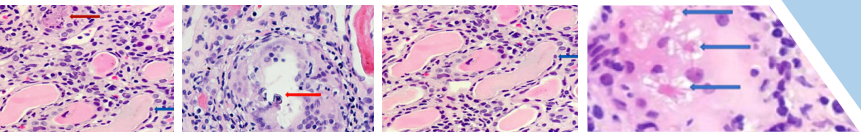

JOURNAL OF CLINICAL AND TRANSLATIONAL NEPHROLOGY (JCTN)

ORIGINAL ARTICLES

Case Report

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CASE REPORT Open Access

KIDNEY WITH LOWER POLE SIMPLE CYSTS – IS IT AN ABSOLUTE CONTRAINDICATION FOR RENAL BIOPSY?

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ABSTRACT

A percutaneous renal biopsy is an essential tool for diagnosis, prognosis, and choice of treatment for primary and secondary renal disease, as well as transplant kidney. It is a core procedure of nephrologists done under ultrasound-guided. The lower pole of the left kidney is our usual approach as the risk of injury to the major vessels will be very minimal. However, the presence of renal cyst at the lower pole of the kidney may increase the difficulty of renal biopsy as there is the possibility of puncturing the renal cyst during the procedure causing unstoppable bleeding. Here we present two case reports in which we were able to do percutaneous renal biopsy under ultrasound-guided for patients with simple renal cysts at the lower pole of the kidney without causing any significant complication. In the hand of expert personnel, a lower pole cyst can be avoided under ultrasound-guided biopsy.

INTRODUCTION

Imaging guided percutaneous renal biopsy is an essential tool used to establish the diagnosis of the cause of focal renal lesion, unexplained renal impairment or renal transplant rejection. The first radiographic guided renal biopsy was performed in 1944 by Nils Awall, and was later published in the literature in 1955 by Iversen and Brun (1). Instead of using a sitting position which was described in the 1950s, nowadays, a kidney biopsy is usually performed in the prone position. The lower pole of the left kidney is the preferred site for kidney biopsy as the risk of injury to the major vessels will be minimal, and any damage to the liver can be avoided (2). The presence of a renal cyst, especially at the lower pole, will increase the difficulty of getting adequate renal tissue during biopsy without puncture the renal cyst. This is one of the common dilemmas we faced during the procedure, and at times we might even have to cancel the biopsy as the risk might outweigh the benefit. Here we report two cases that renal biopsy where we have demonstrated that can we have successfully biopsied two kidneys with lower pole cysts without any significant complications.

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FIRST CASE REPORT

A 27 years old lady, with underlying lupus nephritis diagnosed at ten years old, was referred from another hospital for the continuation of care since April 2019. She was put on mycophenolate mofetil for eight years but only achieved partial remission with urine protein creatinine index ranging from 0.1 g/mmol to 0.3 g/mmol. Over six months of subsequent follow-up, her urine protein creatinine index was noted to have progressively worsened to 0.38g/mmol despite being compliance with the medications. Hence she was counselled for a repeat renal biopsy. Her creatinine level remained normal (79µmol/L) with eGFR 88.4 ml/min/1.73m^2. Ultrasound kidney was performed before the renal biopsy. Ultrasound report showed that the right kidney size of 9.59cm with cortical thickness 1.05cm and left kidney size of 10cm with cortical thickness 1.4cm (figure 1.1). Both showed an increase in echogenicity. There were also two simple

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cysts seen at the lower pole of the left kidney measuring 1.1cm x 1.0 cm and 0.7cm x 0.5cm. There was no solid component, internal septation or wall calcification seen within the renal cyst. A decision was made to biopsy the left kidney instead of the right kidney as the right kidney was relatively smaller and more difficult to approach compare to the left kidney. By using real-time ultrasound-guided, a left lower pole renal biopsy was performed using the biopsy gun – u2013 Bard Magnum. Two cores of renal tissues were obtained without puncturing the renal cyst. There was no immediate complication after renal biopsy,

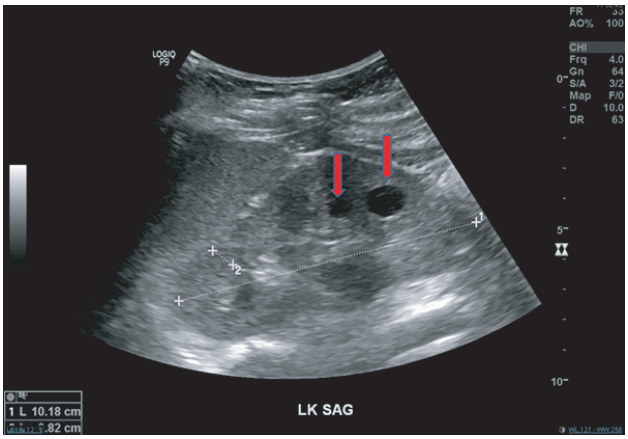

Figure 1.1 Ultrasound image of the left kidney. It showed bipolar length of 10.18cm with cortical thickness of 1.4cm. There were two renal cysts (red arrows) seen at the lower pole of the kidney.

and there was no perinephric hematoma detected. She was put on bed rest for six hours, and all three samples of her urine collections were clear. She was allowed home the same day. Her creatinine level was 87µmol/L with eGFR 78.7 ml/min/1.73m^2 during the clinic follow up.

There was a total of 7 glomeruli in the planes section of the renal biopsy sample. The biopsy results showed focal active proliferative and sclerosing pattern with mild to moderate mesangial hypercellularity, in keeping with ISN/RPS class III/V (A/C) lupus nephritis. Mild chronic tubulointerstitial damage and mild hypertensive vascular damage was detected. With the information obtained, her immunosuppressants were modified accordingly.

SECOND CASE REPORT

The second case was a 35 years old lady referred from another hospital for recurrent microscopic hematuria. She had a normal creatinine level (65µmol/L) with eGFR 105.8 ml/min/1.73m^2. She was a potential kidney donor for her husband, who was on regular hemodialysis. She had no family history of kidney disease. Ultrasound kidney done showed that there was a cyst measuring 1.1 x 0.9cm at the lower pole of the left kidney (figure 2.1), with bipolar length 9.2cm and parenchymal thickness 1.3cm. The right kidney bipolar length was 9.3cm and parenchymal thickness was 1.3cm. She was advised for a renal biopsy for investigation of the microscopic haematuria because of the fact she was a potential kidney donor. We managed to obtain two cores of renal tissues under real-time ultrasound-guided via a u2013 Temno biopsy gun. There was no immediate complication seen after the renal biopsy. However, she developed a transient gross hematuria post renal biopsy, which subsequently cleared up after 24 hours. Her haemoglobin level remained static (11-12g/dL), and repeated ultrasound post renal biopsy showed small perinephric hematoma measuring 0.8cm x 3.8cm at the lower pole of the left kidney and the preserved lower pole renal cyst (figure 2.2). She was allowed home one day later after renal biopsy. Her creatinine level remained the same (which was 64µmol/L) before discharge. Her renal biopsy report showed a total 18 glomeruli in plane sections with minimal change in light microscopy and mild tubulointerstitial changes. She was currently continuing her transplant workup in the referring hospital.

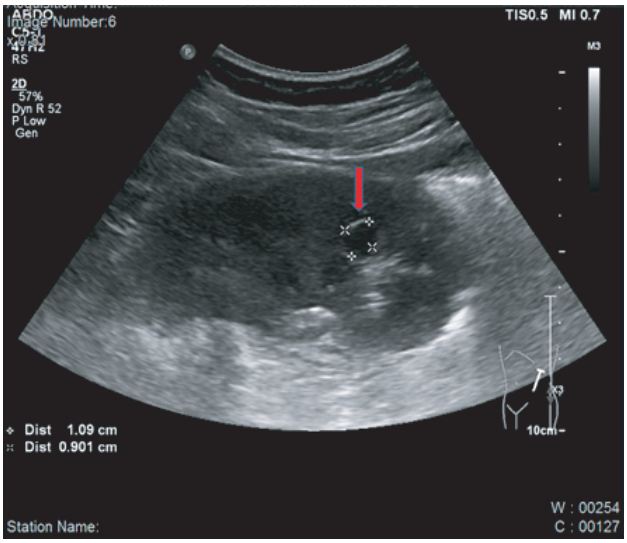

Figure 2.1 Ultrasound image of the left kidney pre-biopsy. There was a renal cyst (red arrow) measuring 1.09cm x 0.90 cm, located at the lower pole of the left kidney.

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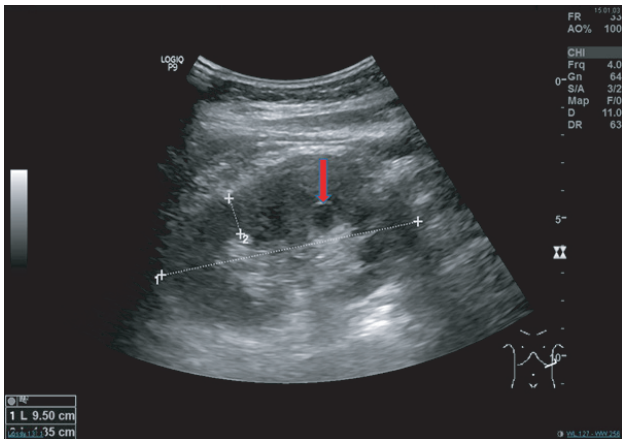

Figure 2.2 Ultrasound image of the left kidney post renal biopsy. There was small perinephric hematoma measuring 0.8cm x 3.8cm over the lower pole of the kidney. The renal cyst at the lower pole (red arrow) remained the same.

DISCUSSION

(figure 2).

Ultrasound-guided renal biopsy using an automated spring-loaded biopsy device is the standard method of kidney biopsy in most of the region. By using this technique, more than 99% of the renal sample was enough for diagnostic, and it also significantly reduced life-threatening complications from 0.12 to 0.02%. (3) Multiple renal cysts, especially at the lower pole, remained a big challenge for renal biopsy as the lower pole of the kidney is the preferred site for renal biopsy to avoid injury to the major vessels. So far, no study or guideline is mentioning what is the most appropriate approach when the presence of cyst at the lower pole of the kidney. Laparoscopic renal biopsy is the alternative method, especially in the presence of multiple renal cysts as homeostasis is better to achieve under direct view (2). Other alternative approaches include CT guided biopsy and transjugular method. The limitation for CT guided biopsy is that it does not assess any possible movement of the kidney related to breathing during the procedure. Similarly, a transjugular approach has a lower diagnostic yield due to the fact that biopsy needle has to pass through the medulla first, often resulting in inadequate glomeruli (which mainly in the renal cortex) in a tissue sample (4).

Even if the renal biopsy is a relatively safe procedure, it is not without complication. Minor complication includes asymptomatic haematoma, microscopic or gross haematuria, pain > 12 hours, perinephric infection, arteriovenous fistula and anaemia with haemoglobin drop > 1g/dL. Major complications comprise of expanding hematoma requiring blood transfusion, urinary tract obstruction with or without acute kidney injury, hypotension related to bleeding, sepsis, nephrectomy, and death (4).

Though bleeding is the primary concern for this procedure, systemic review and meta-analysis showed that the risk is minimal. In essence, transient gross haematuria risk happened in 3.5% of cases, the need of transfusion therapy was 0.9%, embolization occurred in 0.6% of cases, nephrectomy for control of bleeding was 0.01%, and death risk was 0.02% (5).

In our case report, we showed that even in the presence of simple renal cysts at the lower pole of the kidney, a renal biopsy could be performed safely under real-time ultrasound-guided without puncturing the renal cysts. Though in the second case report patient developed gross hematuria post renal biopsy, it was a minor complication as no blood transfusion was required, and the patient was allowed home after 24 hours. Nevertheless, we suggest that percutaneous renal biopsy should be performed by experienced personnel and with necessary precautions if presence of renal cyst. Risk of complication is still relatively higher compare to those without renal cyst. Urology and interventional radiology back up are needed if complications occur.

CONCLUSION

Renal biopsy using ultrasound-guided is a safe procedure and the major complication is rare. Despite the conventional relative contraindication for renal biopsy in a cystic kidney patient, it still can be done safely by the skillful personnel using real-time ultrasound-guided, and it must be done in the facility equipped by urology and interventional radiology back up to ensure any possible mishap managed accordingly.

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REVIEW ARTICLE Open Access

SERTRALINE FOR THE TREATMENT OF DEPRESSIVE SYMPTOMS IN CHRONIC KIDNEY DISEASE COMPARED TO PLACEBO: A LIMITED SYSTEMATIC REVIEW

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ABSTRACT

Background: Depressive symptoms have been associated with chronic kidney disease and linked to increased morbidity and mortality. Sertraline, a selective serotonin reuptake inhibitor (SSRI) is widely used in general population. However, evidence of its effectiveness in chronic kidney disease patients is still lacking.

Aim: To examine the effectiveness of sertraline compared to placebo in treating depressive symptoms in chronic kidney disease.

Methods: Systematic review. Search was performed using five databases; PsychoINFO, Medline, Embase, SCOPUS, PUBMED, until September 2019. Inclusion criteria were randomized controlled trials, minimum of 6 weeks and outcomes measured using validated tool measurements. Citation tracking and hand searching were also performed. The included studies were assessed using Grading of Recommendations Assessment, Development and Evaluation for quality and risk of bias.

Results: The literature search yielded 687 publications; 3 randomized controlled trials were included. A total of n=142 (n=15 to 102) patients were randomized to receive treatment with sertraline. Trial durations were 8, 12 weeks and 6 months. There were no differences for non-dialysis population; score changed by -4.1 in sertraline group and -4.2 in placebo group(p=0.82). Two studies involving hemodialysis patients showed improvement in scores; from 24.5+4.1 to 10.3+5.8 ($p<0.001$) and 23+11 to 22.5+9; a reduction of 0.5+5 ($p<0.001$). However, both trials were of low quality. Non-uniformity of assessment tools used for measurements precluded meta-analysis.

Conclusion: Current available evidence does not demonstrate the effectiveness of sertraline as treatment for depressive symptoms in chronic kidney disease patients. Future trials are required and should be considered as research priority.

Keywords: Sertraline, Depression, Chronic Kidney Disease

INTRODUCTION

Chronic Kidney Disease (CKD) is prevalent and estimated in almost 10% of the general population. CKD is defined as "abnormalities of kidney structure or function, present for >3 months, with implications for health" and it is divided into stages 1 to 5 based on estimated glomerular filtration rate (1). Patients with end-stage renal disease (ESRD) or Stage 5 CKD experience high symptom burden and these symptoms are largely under-recognized (2).

Depression has been recognized as the most frequently encountered psychiatric disorder in ESRD patients. Depressive symptoms at the initiation of dialysis have been associated with short, mid and long-term mortality (3). The prevalence of depression in ESRD patients ranges from 14.7-76% (4,5). Although antidepressants have a role in treating depression in physically ill patients, evidence for its use in dialysis patients is sparse and inconclusive (6,7). Pre-dialysis patients (CKD Stages 3-5) have been reported to have a high prevalence of depression (47.1%) (8). This has been linked with morbidity, treatment

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adherence, hospitalizations and mortality (9–11). Antidepressants are used one and a half times more in CKD patients compared to the general population despite lacking evidence of its effectiveness in the literature (12). The relationship between CKD and depression is complex and not fully understood; its pathophysiology described to be "bidirectional and multifactorial" (13).

SSRI is recommended as the first line treatment for the management of depression in adults by published clinical practice guidelines (14,15). SSRIs have favorable effects on immune system regulation, increase serotonin concentration, possibly anti-inflammatory and anti-oxidative effects (18). Sertraline; a type of SSRI has been recommended as it is cheap and efficacious when compared to other anti-depressants (16). It has been used since the 1980s, easily available, tolerable and does not require dose adjustments in CKD (17). It is biochemically "designated as (1S,4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthylamine and contains two asymmetric carbon atoms" (19). It's pharmacokinetic properties allows "consistent correlations between dose and peak plasma concentrations in doses used clinically (ranging from 50-200mg/day)" (19). It is substantially absorbed through first-pass metabolism with less than 1% excreted unchanged in urine (19). Sertraline was reported as the third commonest SSRI used in CKD patients (12).

Reviews addressing treatment options for depressive symptoms in CKD patients to date excluded patients who were not receiving dialysis and did not focus on sertraline. Therefore, this review aims to examine the effectiveness of sertraline in treating depressive symptoms in adult patients with all stages of CKD compared to placebo.

MATERIALS AND METHODS

The outline of this systematic review was performed in accordance to PRISMA guidelines (20).

Search strategy and study selection

Five databases were used for the search; PsychoINFO (1806 to September Week 2, 2019), Ovid Medline (1946 to September 19, 2019), Embase (1974 to Week 38, 2019), SCOPUS and PUBMED. Citation tracking and hand searching were also performed. The search was conducted up to and including the 21st of September 2019. List of words used for the search is outlined included depressive symptoms (keywords were depression, depressive symptoms, mood disorders, depressive disorders, mental health, mental disorders) AND Chronic Kidney Disease (keywords were renal dialysis, renal insufficiency, kidney disease, haemodialysis, peritoneal dialysis, renal failure, kidney failure) AND sertraline.

Data extraction

A data extraction form was developed to summarize characteristics of included studies; information collected for this purpose include general information, methods of study, risk of bias assessment, study characteristics – participants, interventions and comparisons, outcomes, data, and results. These data were extracted by one reviewer for this systematic review.

Inclusion Criteria	• Adult (aged ≥ 18 years); patients fulfilling criteria of CKD including dialysis and non-dialysis with depressive symptoms. Depressive symptoms assessed by at least one self-reported using validated questionnaires and/or interviews fulfilling criteria of diagnosis of Depression (using DSM criteria) • Use of Sertraline for the treatment depressive symptoms with clear details of treatment provided and reports on the doses used. • Randomized Controlled Trial designs • Duration of at least 6 weeks • Outcomes (primary and secondary) of depressive symptoms measured using validated tool assessments with measurements at pre and post-intervention. • Availability of full paper and published in the English language • Comparison arm: placebo
Exclusion Criteria	• Retrospective Trials, Quasi-Experimental trials, Case Series. • Editorials, Grey Literatures (Thesis, Dissertation, Conference Proceedings) • Transplant patients • Papers that used other types of antidepressants, examining a class effect and not-specifically the effects of Sertraline.

Table I: Criteria for inclusion and exclusion

Quality Assessment

Each study was analyzed thoroughly and quality of evidence was assessed using "The Grades of Recommendation, Assessment, Development and Evaluation Working Group" (GRADE) (21).

Data Analysis

There were variations in the reporting of outcome measurements. Two studies reported scores of depression but different measurement tools were used. One study used the change of scores from baseline; but did not report on the actual scores at the end of the study. Different validated tools were used to assess the outcomes of depressive symptoms; 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-C16) (22), The Beck Depression Inventory (BDI) alone (23) and a combination of BDI with Montgomery–Asberg Depression Rating Scale (MADRS) (24). These factors precluded a meaningful meta-analysis; therefore, the analysis reported was primarily descriptive.

RESULTS

Results of the search

The initial search yielded 687 articles before 145 duplicates were removed. Eligibility of 33 articles was identified for full review of publication; with the final inclusion of 3 trials (figure 1).

Description of studies

Three RCTs were included and characteristics outlined in Table II. A total of n=142 (n=15 to 102 participants in each trial) CKD patients received treatment with sertraline. The trials were of 8- and 12-weeks' and six months' duration. Two out of three were trials performed in hemodialysis patients and one examined CKD non-dialysis population. Male gender was predominant in all three RCTs (57-76.6%). These studies were conducted in the United States, United Kingdom and Iran.

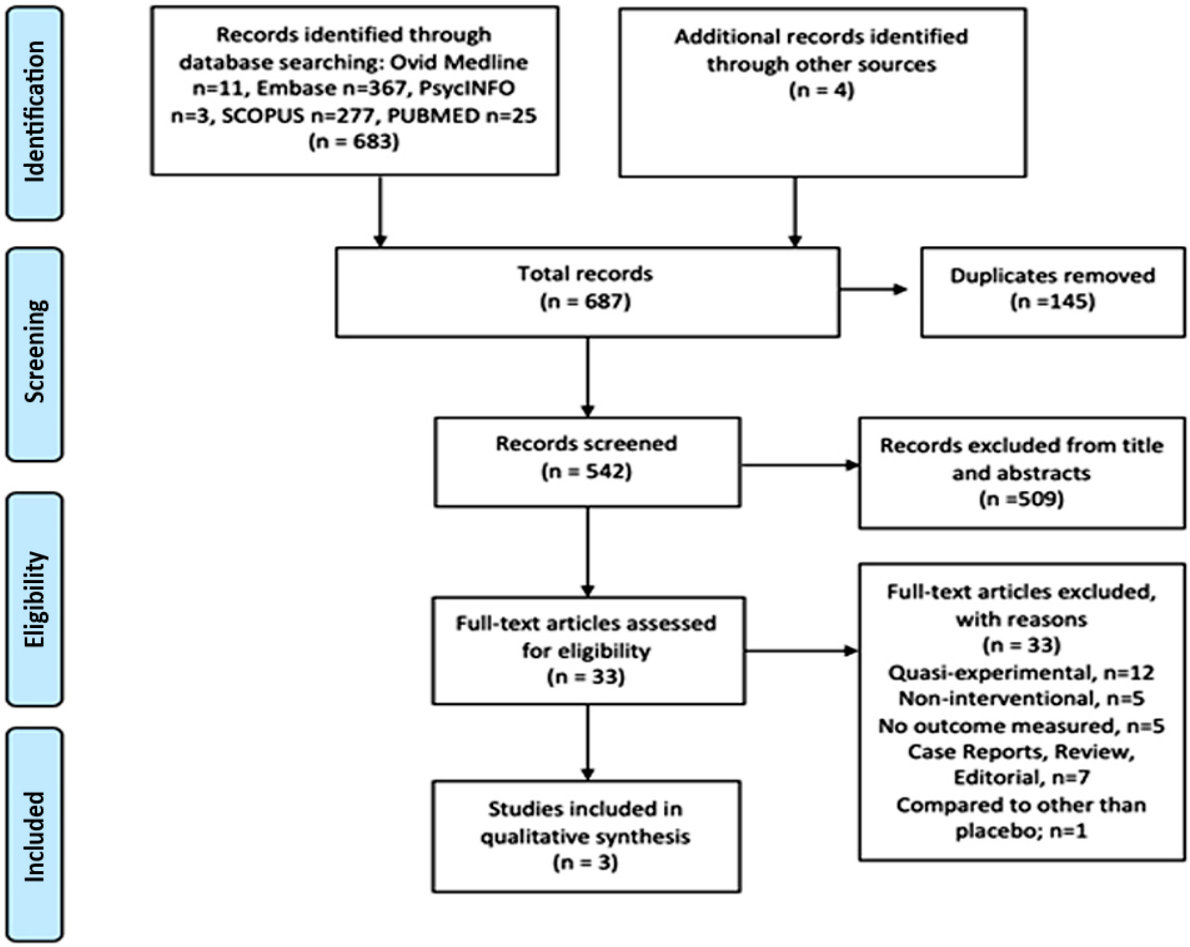

Fig 1: PRISMA Flowchart

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Author (year), country, quality score	Description of intervention and details of follow up	Eligibility	N at baseline, attrition rate	Sample characteristics
Taraz 2013 (23) Country: Iran, 1 centre GRADE Score: 1 (Very Low	Design: Randomized, double blind, placebo controlled i. Sertraline 50mg or placebo first 2 weeks and then titrated up to 100mg for following 10 weeks. ii. Pre-dialysis blood samples taken at week 6 and 12 from arterial port of dialysis access. iii. Duration of follow-up: 12 weeks	Adults 18 and 80 years; at least 3 months on Hemodialysis (HD) using AV fistula Diagnosis of Depression based on the Beck Depression Inventory II (BDI-II) >16 Patients' HD prescription standardized – 4 hours 3 times per week, same type of dialysis membrane, dialysate and vascular access (no details given). Single HD centre	N=50 **Sertraline n=25** Placebo n=25 43/50 (86% attrition rate) completed follow-up. 21/25 patients in Sertraline arm completed study. Analysis by intention-to-treat.	Age 60 (22) Male 12/25 (57%)
Friedli 2017 (24) Country: United Kingdom, 5 centres GRADE Score: 2 (Low)	Design: Multi-Center, Randomized, Double Blind, placebo-controlled trial i. Initial dose of Sertraline 50mg with assessment by psychiatrist at baseline, 2 weeks and 2, 4 and 6 months. An option of increasing dose to maximum of 200mg at 2 and 4 months if indicated. ii. Monthly review by research nurse. Follow up 2 weeks, 2, 4 and 6 months	Age > 18 and receiving HD treatment for more than 3 months Screening: BDI scores > 16 Referred for interview by psychiatrist using MINI Interview to confirm presence of Major Depressive Disorder. Five renal units in Midlands and Southeast England, United Kingdom.	N= 30 **Sertraline n=15** Placebo n = 15 21 completed trial (70% attrition rate) 8/15 in Sertraline arm and 13/15 in placebo.	Age 61.7 (13.2) Male 11/15 (73%)
Hedayati 2017 (22) Country: United States of America, 3 centres GRADE Score: 4 (High)	Design: Randomized double-blind placebo-controlled trial i. Sertraline starting dose of 50mg/day and escalated to a maximum dose of 200mg/day based on tolerability and response. ii. Follow-up every 2 weeks for 6 weeks then every 3 weeks for the remaining 6 weeks. iii. 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-C16) scores, questionnaire assessed and filled by trained personnel. Blood and urine samples at baseline and week 12.	Stage 3, 4, 5 CKD non-dialysis, estimated glomerular filtration rate (eGFR) of < 45 mL/ min/1.73m2 Screening: QIDS-C 16 > 11 Mini International Neuropsychiatric Interview based on Diagnostic and Statistical Manual of Mental Disorders (Fourth edition) to confirm diagnosis	N=201 **Sertraline n=102** Placebo n=99 N=97 completed the trial in the Sertraline arm Attrition rate 84% 193 included in primary analysis (97 in Sertraline and 96 in placebo) Median treatment duration 84 days Median eGFR was 27.5 mL/min/1.73	Age 57.7 (14.5) Male 74/97 (76.6%) CKD Stages: Stage 3A 11% Stage 3B 36% Stage 4 36% Stage 5 17%

Table II: Characteristics of Included Studies

Outcome measurement tools, definition of outcome and its measures	Continuous Outcome Results		Significance & Comments
	Sertraline arm	Placebo Arm	
BDI-II Values in median (interquartile range) and mean +SD Response was defined as more than 50% reduction in BDI scores	Baseline: 29 (13) 6 weeks 21(11.5) 12 weeks: 15 (5.5) **Sertraline** significantly improved depression in 10/21 patients (47.5%)	Baseline: 23 (11) 6 weeks 22.5 (8.5) 12 weeks: 22.5 (9)	p=0.243 p not available p<0.05 BDI-II score reduction of -11.3+5.8; compared to placebo of -0.5+5, p<0.001
Montgomery–Asberg Depression Rating Scale (MADRS) Mean (SD) values Mean change in MADRS score over 6 months Mean change in BDI scores over 6 months	Baseline (n=15) 24.5 (4.5) 2 months (n=9) 13.9 (5.8) 4 months (n=8) 10.6 (6.6) 6 months (n=8) 10.3 (5.8) -14.5 (95% CI -20.2 to -8.8) -15.7 (95% CI, -24.3 to -7.1)	Baseline (n=15) 25.3 (4.2) 2 months (n=14) 15.8 (4.8) 4 months (n=13) 11.1 (5.5) 6 months (n=13) 10.9 (5.1) -14.9 (95% CI, -18.4 to -11.5) -13.0 (95% CI, 19.6 to -6.4) Large CI without any details given	Between group difference: -1.9 (-6.5 to 2.7) p not available -0.45 (-6.0 to 5.1) p not available -0.67 (-5.7 to 4.4) p not available Overall MADRS scores reduced from 24.9+4.3 to 10.7+5.2 (p<0.001) Overall BDI II for both groups: 29.1+8.4 to 17.2+12.4 (p<0.001) Both arms improved at 6 months; with no statistical difference
Scores mean (95% CI) Difference in QIDS-C16 scores at end point Response defined as decline > 50% in the baseline QIDS-C16 score Remission rates (defined as reduction of QIDS-C16 score to <5)	Baseline: 14.0 (2.4) -4.1 (-5.1 to -3.1) 31/97 32% 15/97 15.5%	Baseline: 14.1 (2.4) -4.2 (-5.0 to -3.5) 24/96 25% 14/96 14.6%	Between group difference, mean (95% CI) 0.1 (-1.1 to 1.3), p=0.82 7.0 (−5.7 to 19.6), p=0.28 0.9% (−9.2% to 11.0%), p=0.86. No treatment group main effect (p= 0.57) or interaction with time (p=0.58) in terms of remission

Table II: Characteristics of Included Studies *(cont')*

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Quality of evidence and risk of bias

Hedayati et al was graded as good quality; although there were initial concerns on heterogeneity of patients' inclusion criteria. An inclusion criteria of CKD stages 3 to 5 will result in a wide range of patients. The estimated glomerular filtration rate was subsequently brought down to 45mL/min/1.73m2 (22).

Fredli et al was graded as low quality due to many factors that arose from an inadequate sample size. The intended size of participant was not achieved due to recruitment issues. There was selection bias as they included patients who could read and write only in English using a self-filled questionnaire as a screening tool and post-intervention assessment (24). The attrition rate was 70% (attrition bias); with only 53% of the patients in the intervention arm completed the 6 months' follow-up (24).

Taraz et al was graded very low quality; this study did not report the process of blinding (other than allocation). There was high risk for selection, detection, publication bias and the published material was different from the registered protocol (25).

Effects of intervention

Out of the 3 RCTs; 2 did not show any significant difference in depressive symptoms compared to the placebo arm (22,24). One RCT demonstrated improvements of depressive symptoms in only 10/21 (47.5%) patients despite an overall improvement in depression scores (23). CKD non-dialysis population showed no significant difference in both sertraline and placebo arm despite an overall reduction of depressive symptoms scores measured by QIDS-C16 [changed by -4.1 in the sertraline group and -4.2 in the placebo group (p=0.82)] (22). There was no treatment group main effect (p= 0.57), interaction with time in terms of remission (15.5% in sertraline and 14.6% in placebo, p=0.58) and response (32% in sertraline group and 25% in placebo, p=0.28). The majority of the participants of this study (84%) were unemployed and 22% had a history of drug abuse (22).

Friedli et al reported results of overall improvements in both sertraline and placebo. Overall MADRS scores reduced from 24.5+4.1 to 10.3+5.8 ($p<0.001$) and BDI-II scores reduced from 29.1+8.4 to 17.3+12.4 ($p<0.001$) (26). There was a significant overall reduction from baseline scores at 6 months in both MADRS and BDI scores. However, there was no significant difference between both groups [mean change in MADRS scores were -14.5 (95% CI, -20.2 to -8.8) in sertraline group and -14.9 (95% CI, -18.4 to -11.5) in placebo group]. This study had 2 phases and did not achieve the intended sample size (24).

Taraz et al showed overall improvement of depressive symptoms using BDI-II assessments in sertraline arm. A significant reduction ($p<0.001$) was reported [11.3+5.8; from 29 (13) to 15 (5.5)] compared to placebo [0.5+5 23 (11) to 22.5 (9)] (23). However, despite an overall reduction, less than half of the patients (10/21) showed improvement in depression scores (23). In this study, biochemical results of haemoglobin (10.9+0.8 and 11.5+0.56, p=0.012) and serum albumin (4.1+0.2 and 4.4+0.3, p=0.006) were found to be significantly lower in the placebo group at week 12 as compared to sertraline arm (23).

Side effects

There were concerns on side effects reported by two studies (22,24). Friedli et al reported 6/15 dropouts in the first 2 months; one who had died and 3 participants withdrew because of side effects (24). Similarly, Taraz et al reported 3/25 participants withdrew because of side effects, 1/25 died during follow-up and only 21/25 completed the trial in the intervention arm (23). Hedayati et al did not demonstrate differences in adverse events between the intervention and placebo group. Both groups had 3 patients (3.1%) who withdrew because of side effects. There was significantly higher incidence of gastrointestinal side effects reported in sertraline group (22).

DISCUSSION

To the best of the author's knowledge, this is the first systematic review that focuses on sertraline use and its effectiveness in CKD population. The findings from the included trials did not demonstrate its effectiveness. Depression is common in CKD patients; both in dialysis and non-dialysis population. The lack of standardization in diagnosis, inclusion criteria and tools for measurement of outcomes may be possible explanations. Diagnostic tools and measurement outcomes will need to be standardized for future use; both clinically and in research. Diagnosis of depression may not be straightforward as symptoms may overlap with that of uremia (27). The gold standard of diagnosis remains through clinical interviews with the presence of five or more symptoms following the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (28). For CKD population, several questionnaires have been validated to be used as screening tools. As depression is largely under-recognized in these populations of patients, routine screening had been suggested (29). However, it has yet to be incorporated into standards of care and this practice remains controversial (29). There is a need for close collaborations between clinicians in the field of nephrology and psychiatry to address standardization of diagnostic tools. Future research will need to account for

trajectory of disease to enable meaningful interpretations of results.

This systematic review included population of patients who were on haemodialysis and CKD stages 3-5; but there was no representation of peritoneal dialysis population. Conflicting results were found in published studies of peritoneal dialysis patients which did not meet the inclusion criteria of this systematic review. Published reports supported the use of sertraline but trials were non-randomized. These include two were case series involving n=10 (30) and n=25 patients (31) and two studies that did not report clear measurements of pre and post-treatment results (32,33). These conflicting results suggest possible differences in the effectiveness of sertraline in patients on haemodialysis and peritoneal dialysis; however, this will require in-depth examinations.

Prevalence of depression in dialysis patients undergoing both modalities of dialysis is high and it has been associated with mortality (34). Mechanisms that have been suggested by which depression could lead to poor outcome in CKD patients include increased inflammation (35,36), cognitive impairment (37), poor nutrition (38), non-adherence to therapy and high interdialytic weight gain in hemodialysis patients (39). Effects on pro-inflammatory and cytokines has been proposed to explain the effectiveness of sertraline in managing pruritus in dialysis population (40,41). Depression has been associated with elevated interleukin-6 than other cytokines in the dialysis population; however, the possibility of a causal relationship between depression and inflammation is still uncertain (42). Although continued research had increased the understanding of the pathophysiology of depression, precise mechanism(s) is still incompletely understood at present. This may explain its proven effectiveness in pruritus; but not demonstrated in depression.

The lack of efficacy could be due to the presence of multiple confounders in a complex disease such as CKD. Patients with CKD have many co-morbidities, different etiologies and potential causes of depressive symptoms. Bidirectional relationship of CKD and depression needs further clarification and in-depth research.

This systematic review raised concerns on its side effect profile. Sertraline has been reported to have value in improving intradialytic hypotension (43) and had reported a rare but serious side effect of serotonin syndrome (44). When dealing with CKD patients, drugs may have interactions with a pre-existing list of medications (45). In view of these, non-pharmacological treatment can be considered as an alternative and may prove to be an important option in management. Potential benefits were demonstrated using non-pharmacological treatment; such as increasing frequency of hemodialysis sessions, cognitive behavioral therapy and exercise programs (46). However, a recently published randomized controlled trial reported significant improvement in depression scores in sertraline group when compared to patients who had cognitive behavioral therapy at 12 weeks (47). Hence, the use of sertraline in CKD patients will need to be individualized and tailored to their clinical needs.

A few limitations were recognized for this systematic review. Only one person performed all the literature search; this may increase the errors in data handling despite repeated meticulous data checking. The search could have been widened by using more relevant keywords. The number of studies included was small and results may not be replicable and generalizable. Peritoneal dialysis patients have been reported to have clinical depression but were not represented in this review (48). Two trials included were on haemodialysis patients (7). Patient profiles are different across CKD stages 3 to 5 and treatments (hemodialysis and peritoneal dialysis); these can be associated with different potential confounders making the interpretations of results challenging

Clinical and future research implications

A more holistic approach in managing CKD patients with depressive symptoms needs to be taken. Professionals from psychiatry, nephrology and palliative care should come together and work towards standardization of assessment, evaluation and management specifically for CKD patients with depressive symptoms. Recruitment in trials addressing depression in CKD may be difficult, especially in the dialysis population as chronically ill patients are reluctant to participate in clinical trials (49). With these difficulties in mind, different angles need to be considered. A prospective trial commencing from early stages of CKD would be ideal to answer these questions and the use of big data may be reasonable given these difficulties. These trials will need to be multi-centered, include a large number of participants to account for the foreseeable high dropouts and withdrawals (from various reasons including consent, side effects, death) due to the complexity of CKD patients.

CONCLUSIONS

The effectiveness of sertraline in treating depression in CKD patients is not demonstrated. Literature was scarce and of low quality. As depression is prevalent in CKD patients, large randomized controlled trials are required and should be considered as an area of research priority.

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DECLARATION OF INTEREST

The author declares no conflict of interest.

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REVIEW ARTICLE Open Access

ISOLATED RENAL SARCOIDOSIS WITH ACUTE KIDNEY INJURY - A RARE ENTITY

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ABSTRACT

Sarcoidosis is a multisystem inflammatory disorder that commonly affecting the lungs. However, isolated renal sarcoidosis without lung involvement is a rare condition. Sarcoidosis is known to cause kidney involvement via different mechanisms. Hypercalcemia and hypercalciuria may trigger renal stones formation and result in obstructive uropathy. Sarcoidosis can also cause interstitial nephritis with or without granuloma formation in the kidneys. The true incidence of renal involvement in sarcoidosis is unknown as renal biopsy is not routinely performed unless there is presence of renal impairment. Renal sarcoidosis is a diagnosis of exclusion supported by the typical histopathological findings. Due to the scarcity of this disease, there is no universal guideline or recommendation regarding the diagnosis and treatment for renal sarcoidosis. Here we present a case that initially presented to us with rapid deterioration of kidney function, which was later proven to be renal sarcoidosis, followed by a literature review.

Keywords : renal, sarcoidosis, literature review

INTRODUCTION

Sarcoidosis is an inflammatory disease of unknown aetiology characterized by intense cell-mediated immune reaction and granuloma formation. It is often diagnosed by clinical manifestations and radiographic features, with the presence of non-caseating granuloma. It is a multisystem disorder that mainly involves lung in more than 90% of the cases. However, it may also affect the heart, skin, eyes, kidney, and central nervous system (1). Isolated renal sarcoidosis is rare, and renal involvement can be initiated via multiple pathways, which include hypercalcemia and/or hypercalciuria, granulomatous interstitial nephritis, glomerulopathy, tubular dysfunction, as well as obstructive and vascular uropathy (2). A retrospective study done by Javaud el al showed that granulomatous interstitial nephritis appeared to be the most common renal manifestation in sarcoidosis (3). Corticosteroids remain the cornerstone of treatment, especially with the presence of granulomatous interstitial nephritis, and most patients have excellent treatment responses, although the rate of relapse is high. Nevertheless, due to the scarcity of this illness, there is no standardized protocol regarding the optimal dose and the duration of therapy (2).

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CASE REPORT

A 37 years old gentleman was referred from his primary care physician with acute kidney injury. He initially presented with easy fatigue and reduced effort tolerance for the past two weeks. He denied any chest pain, orthopnoea, paroxysmal nocturnal dyspnoea, leg swelling, polyuria, polydipsia, or abdominal pain. He had no medical illness, and none of the family members had similar symptoms or kidney disease. He gave a history of taking traditional herbs in an attempt to alleviate the symptoms but stopped after 3 days. He denied taking alcohol, tobacco, or illicit drugs. He worked as a machine cleaner where he routinely cleaned dust, dirt, grease from the factory machines. When he first presented to his primary care physician, he was diagnosed to have hypertension and was started on losartan/hydrochlorothiazide 50/12.5 mg once daily.

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He was also detected to have renal impairment and was referred to nephrology clinic urgently for further workup and treatment.

During the nephrology consultation, his blood pressure was 121/77mmHg with unremarkable physical examination. Serum creatinine was 374 µmol/L with normal full blood count and fasting blood sugar. There was no eosinophilia in the peripheral blood film. CRP and ESR were normal (2.7mg/L and 13mm/hour). Serum calcium and phosphate levels were 2.22 mmol/L and 1.13mmol/L, respectively. Urine full examination and microscopic examination (UFEME) showed blood 1+ and protein 2+. Hepatitis B/C and HIV screening were negative. Chest radiography showed mild cardiomegaly. There was no perihilar lymphadenopathy seen.

He was admitted immediately for renal biopsy. At the same time, IV methylprednisolone 500mg daily for three days was given as there was high index of suspicion of rapidly progressive glomerulonephritis due to rapid deterioration of renal function with the presence of protein and blood in the urine. Prednisolone was started at 1mg/kg after completion of methylprednisolone. Losartan/hydrochlorothiazide was stopped due to the worsening of kidney function and replaced by amlodipine for blood pressure control. Throughout his stay in the hospital, his serum creatinine level significantly improved from the highest level of 596µmol/L to 429µmol/L after two days and 326µmol/L after one week. His urine protein/creatinine index came back few days later and only showed 0.02g/mmol. His serum C3/C4 level subsequently came back as normal. Antinuclear antibody (ANA), serum p-ANCA and c-ANCA were negative. The serum angiotensin-converting enzyme was 37 U/L (Normal range 16-85 U/L). 24 hours urine calcium was not sent as part of the initial workup because hydrochlorothiazide might affect the result and prednisolone was already initiated.

His renal biopsy showed two cores of renal corticomedullary tissues with a total of 25 glomeruli in a plane of section. Six glomeruli showed global sclerosis and three glomeruli showed segmental sclerosis with glomerular basement membrane wrinkling and periglomerular fibrosis. No glomerular fibrinoid necrosis, membrane thickening,

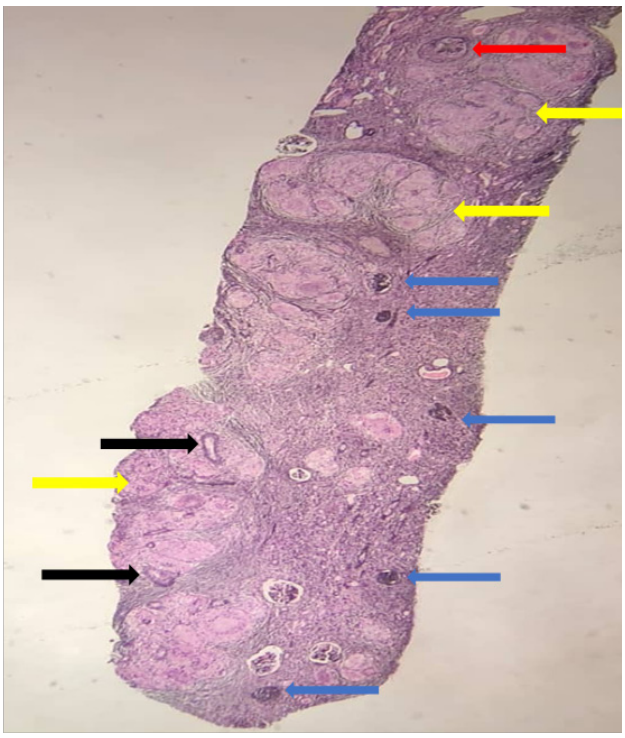

Figure 1: Total of 25 glomeruli identified, six glomeruli show global sclerosis (blue arrow) and three glomeruli shows segmental sclerosis (red arrow). The section also shows granulomas (yellow arrow), thickened vascular channels (black arrow) and a moderate amount of interstitial inflammation, PAAG: 40x.

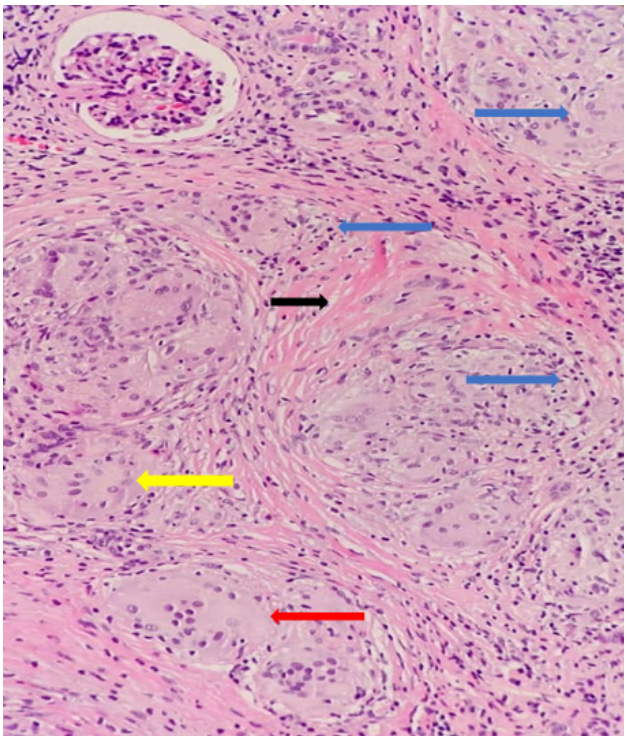

Figure 2: The granulomas are composed of aggregates of epitheloid histiocytes (blue arrow) with the presence of numerous foreign body type (red arrow) and touton type (yellow arrow) multinucleated giant cells. No central necrosis was seen. The surrounding interstitium shows fibrosis (black arrow), and moderate amount of inflammatory cells infiltrate, H&E: 100x.

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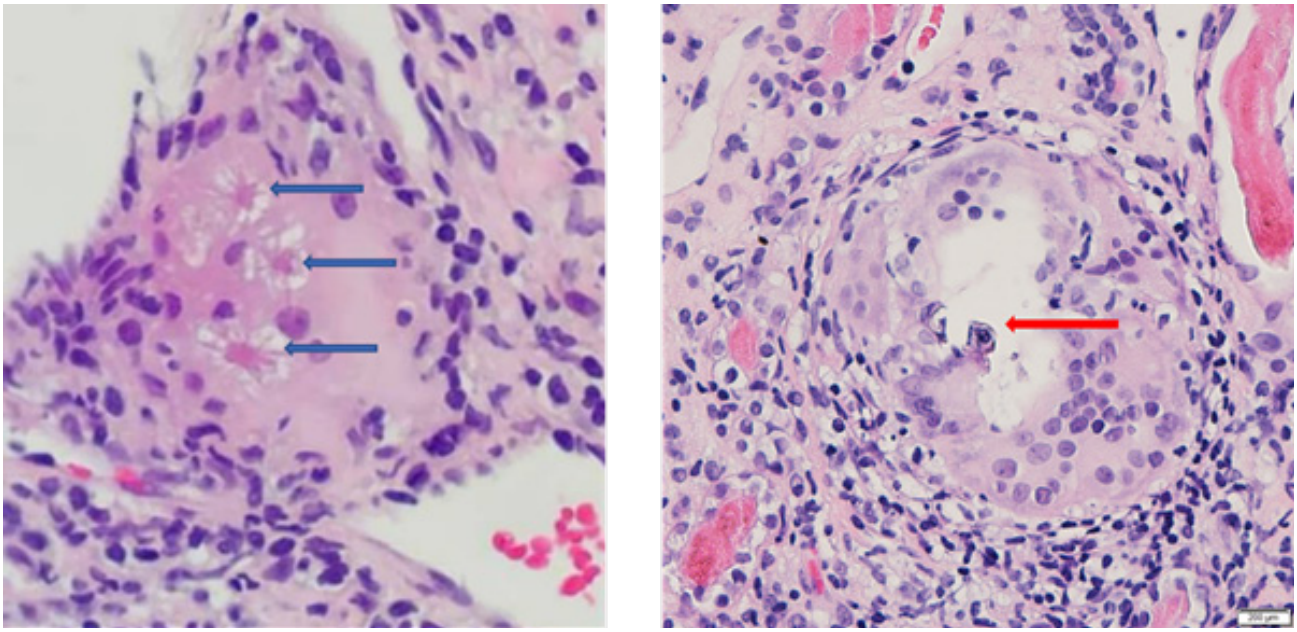

Figure 3: Picture at the left shows Asteroid bodies seen within the granulomas (blue arrow), H&E: 400x. The picture at the right shows single Schaumann like body within the granulomas (red arrow), H&E: 400x.

crescent, or endocapillary proliferation was seen. There were numerous granulomas seen within the cortex and medullary interstitium (figure 1). The granuloma was composed of aggregates of epitheloid histiocytes with the presence of numerous foreign body type and touton type multinucleated giant cells (figure 2).

Occasional Asteroid bodies and Schaumann like body were also noted (figure 3). No central necrosis was noted. The granulomas were predominantly seen surrounding medium and large-sized vascular channels. The vascular channels showed thickened, and hyalinized walls with occasional foci of mild lymphocytic infiltrate within the wall and reactive endothelial lining. The surrounding interstitium of the cortex and medullary region showed dense inflammatory cells infiltrate, composed of histiocytes, lymphocytes, plasma cells, occasional eosinophils, and rare neutrophils. There were focal areas with interstitial fibrosis. The tubules within the cortex were mostly lost, replaced by dense interstitial inflammation and fibrosis. Patchy areas within the cortex and medullary region showed the presence of dilated tubules, lined by reactive epithelium with the presence of occasional mitotic figures. The rest of the tubules within the medulla showed the presence of hyaline and occasional granular cast (figure 4). The lobular and interlobular vessels walls were thickened and hyalinized with occasional foci of mild lymphocyte infiltrate within the wall with reactive endothelial lining, surrounded by aggregates of epitheloid granuloma. No vascular wall fibrinoid necrosis was seen. Immunoperoxidase staining showed a negative result for IgG, IgA, IgM, C3, and C1q. PAS, PAAG, and GMS stains showed the existence of spherical bodies within the granuloma and interstitium. No acid-fast bacilli were seen with Ziehl-Neelsen stain. The morphology is in favour of

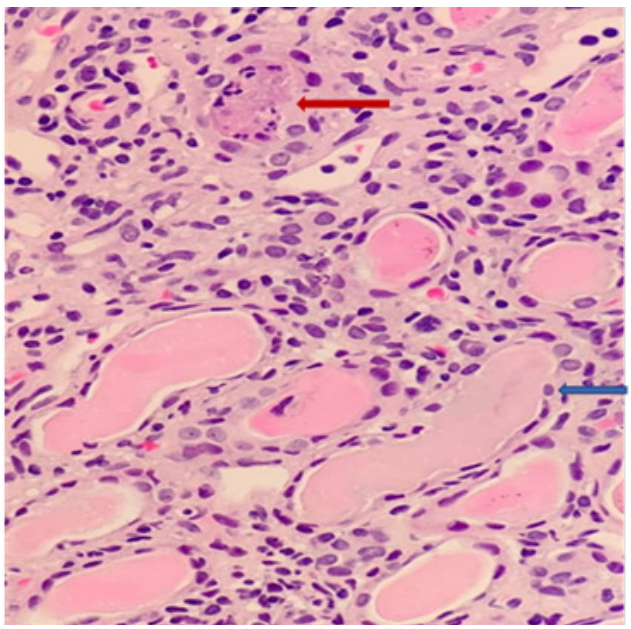

Figure 4: Some tubules show dilatation, lined by flattened epithelium, containing hyaline material (blue arrow) and granular cast (red arrow), H&E: 100x.

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renal sarcoidosis with concurrent acute tubulointerstitial nephritis and hypertensive vasculopathy. He was treated as isolated renal sarcoidosis based on the serology and renal biopsy results even though his serum calcium level was normal as hypercalcemia only presents in up to 34% of confirmed case of sarcoidosis. He did have history of taking traditional herbs, but drug induced granulomatous interstitial nephritis was less likely the diagnosis as his symptoms started prior to the herbal medication. He was discharged well after one week of stay in the hospital. During his monthly follow up in the nephrology clinic, his creatinine level remained stable at 256-258μmol/L. He is currently on a tapering dose of steroids.

DATA EXTRACTION

We carried out a limited qualitative systemic literature review of articles related to renal sarcoidosis from Pubmed, Google scholar, Springer Link and Science Direct. The Scopus index was used to verify the scientific relevance of the papers. Keywords used to search the studies are: 'sarcoidosis', 'renal sarcoid', 'granulomatous interstitial nephritis', 'sarcoidosis interstitial nephritis'. We have included studies that were published in English from years 2007 onwards and excluded those in abstract format only. Case reports or literatures reviews that were published as full articles were included.

DISCUSSION

Sarcoidosis is a multisystem disorder capable of affecting any organ in the body. Though the lung is the most commonly affected organ, screening for potential extrapulmonary involvement should be done in sarcoidosis. Isolated renal sarcoidosis is an uncommon but a well-accepted entity (4-5). Among those with renal sarcoidosis, acute kidney injury occurred in 0.7 to 4.3% of the patients. Out of this, 4 to 10% might develop end-stage kidney disease (ESKD) requiring long term renal replacement therapy (6).

The causes of renal impairment are multifactorial and are thought to include acute interstitial nephritis, obstructive uropathy secondary to nephrolithiasis, retroperitoneal lymph node or retroperitoneal fibrosis, or rarely due to glomerulonephritis (2,6). Interstitial nephritis with or without granuloma remained the most common renal manifestation of sarcoidosis (2,6-7). Mahévas et al. reported that out of 47 cases with biopsy-proven renal involvement of sarcoidosis, 78.7% of the biopsy sample were noted to have non-caseating granulomatous interstitial nephritis (7). The key features of the pathological process in granuloma formation may be due to the immune paradox, which related to the disequilibrium between effector and regulatory lymphocytes, which results in T cells gathering at the disease site. The centre of the granuloma is hypothesized to have poorly degraded antigen, surrounded by macrophages that will subsequently form multinucleated giant cells, with CD4+ helper cells interspersed within it, and CD8+ T cells, regulatory T cells, fibroblasts, and B cells surrounding the periphery (8). Renal sarcoidosis is a diagnosis of exclusion thus when granulomatous interstitial nephritis is identified in renal biopsy other causes need to be ruled out. Wegener granulomatosis, infection such as tuberculosis and fungal infection, TINU syndrome, antibiotics such as penicillin and cephalosporins, anti-inflammatory agents such as ibuprofen, and even post intestinal bypass have been reported to induce granulomatous changes in the kidney (3-4,9). Idiopathic granulomatous interstitial nephritis (GIN) will be the last diagnosis; however, there were several cases reports where the diagnosis of GIN lead to a subsequent diagnosis of sarcoidosis. Thus, it is possible that some cases of idiopathic GIN may represent unrecognized renal limited sarcoidosis (10).

As a result of the overproduction of vitamin D secondary to increased expression of 1-alpha-hydroxylase, hypercalcemia is also one of the common manifestations of sarcoidosis (2,6). Hypercalcemia is reported in 10-34% of patients with sarcoidosis (2,7). The increased vitamin D level causes suppression of parathyroid hormone, which indirectly induces increased renal excretion of the calcium causing hypercalciuria. Hypercalcemia and hypercalciuria lead to nephrocalcinosis and obstructive uropathy due to stone formation. They also induce acute tubular necrosis due to increased intracellular calcium and tubular obstruction secondary to calcium precipitate (2,11). Nephrolithiasis has been detected in 10-13.8% of the patients with the disease (12).

Urinary abnormalities such as proteinuria, microscopic haematuria, and leukocyturia may be present but the absence of these of markers does not exclude renal sarcoidosis (7). Other rare renal presentations of sarcoidosis include glomerular involvement (which can manifest as Ig A nephropathy, membranous nephropathy, focal segmental sclerosis, crescentic glomerulonephritis) and AA amyloidosis (2,11). Renal tubular dysfunction may present as a result of hypercalcemia and interstitial nephritis. Proximal or distal renal tubular acidosis, nephrogenic diabetic insipidus, metabolic alkalosis, or urinary concentration deficits have been reported in various case reports (2,12).

Sarcoidosis is usually a diagnosis of exclusion. Most of the time, the initial presentation is non-specific and vague. The patient can present with fever, fatigue, arthralgia, weight loss, and incidental findings of hypercalcemia and

deranged renal function during routine blood investigations (3-5,7). In the presence of appropriate clinical settings, non-necrotizing granuloma in the tissue sample without the evidence of infection is the usual diagnosis criterion. To establish the diagnosis of renal sarcoidosis, baseline renal function, urinary protein quantification, and calcium excretion as well as serum calcium level should be carried out. Ultrasound kidney should be done especially in patient with elevated serum calcium and urinary calcium excretion as nephrolithiasis or nephrocalcinosis is common (11). Ultrasound examination of the kidneys has sensitivity values of 85-90% to diagnose nephrocalcinosis; hence is the preferred modality compared to abdominal X-ray (12). Angiotensin-converting enzyme (ACE) level may be helpful but is not diagnostic as it is only elevated in 50-57% of cases (6,13). Renal biopsy should be attempted to establish the histopathological diagnosis of renal sarcoidosis, although the absence of characteristic kidney findings does not exclude the diagnosis (14). Interstitial inflammatory cell infiltration with granuloma formation is the most common finding in renal biopsy. Other findings may include glomeruli with focal ischemic tuft retractions, interstitial fibrosis, and tubulointerstitial microcalcifications (6,13,15). A variety of inclusion bodies may be found, which include Asteroid bodies, Schaumann bodies, birefringent crystals, and Hamazaki-Wesenberg bodies (13). These inclusion bodies are neither specific nor diagnostic for sarcoidosis as these can also be found in other granulomatous diseases like tuberculosis. Asteroid bodies are stellate inclusions with numerous rays radiating from a central core, which are being reported in 2-7% of sarcoidosis. Schaumann bodies are large concentric calcifications that form within the cytoplasm of giant cells and being reported in up to 88% of cases (15). Since pulmonary involvement is the commonest manifestation in sarcoidosis, once granulomatous interstitial nephritis is detected on renal biopsy, chest radiography and/or computed tomography (CT) of the chest should be done to evaluate for pulmonary sarcoidosis (1).

Treatment of renal sarcoidosis is focused on the management of hypercalcemia as well as interstitial nephritis (2). Patients with hypercalcemia may present with polyuria and polydipsia due to antidiuretic hormone insensitivity. Thus, the initial treatment of hypercalcemia will be to discontinue any calcium and vitamin D supplementation therapy and provide adequate hydration. A single dose of bisphosphonate could be administered at the same time. Loop diuretics to match hydration will further enhance the urinary excretion of calcium if calcium level remained high after adequate fluids administration (16,17). Glucocorticoids remain the recommended initial treatment as it suppresses the activity of 1-alpha hydroxylase, thus reducing the synthesis of vitamin D. To treat hypercalcemia in sarcoidosis, prednisolone has been recommended to be initiated at a dose of 0.3-0.5mg/kg/day (2). Alternative treatments include hydroxychloroquine and ketoconazole. Both drugs demonstrate the capacity of inhibiting the conversion of 25-hydroxyvitamin D to 1,25-dihydroxy vitamin D. The suggested dose of hydroxychloroquine is 200-400mg/day whereas for ketoconazole is 200-800mg/day (2,17). In addition, dietary intake of calcium should be lowered and reduced exposure to sunlight may provide additional benefits (16).

In the presence of interstitial nephritis, especially the granulomatous type, glucocorticoids remain the most effective treatment at the moment (2,11,17). Intravenous pulse methylprednisolone 500mg-1000mg daily for three days may be given if there is evidence of major organ impairment (2). The recommended starting dose of oral prednisolone is 0.5-1.0mg/kg, and it should be maintained for at least four weeks before tapering down to allow renal function stabilization (2,17). Those who have a poor response to the prednisolone after four weeks of treatment tend to have a poorer renal outcome (2). In the milder form of the disease, prednisolone can be started at 0.5mg/kg once daily (2,17). Prednisolone should be tapered down slowly (e.g. 5mg/week) and maintained at 5-10mg for at least 6-12 months before stopping treatment (2,11). Nevertheless, there were studies that suggested prolonging the treatment duration up to a total of 24 months in view of the high relapse rate especially when the prednisolone is being withdrawn (2). Due to the known adverse effects of prolonged glucocorticoid treatment, initiation of steroid-sparing agents like azathioprine and methotrexate as maintenance therapy have also been suggested (2,11,17). The dose of azathioprine is proposed at 2mg/kg/day (maximum 200mg/day) (17). Methotrexate with folic acid supplementation is another second-line treatment, with extra caution in use, especially in women of childbearing age since it is teratogenic. The recommended dose of methotrexate is 10-20mg/week (2,11,17). There is a higher probability of methotrexate toxicity in those patients with eGFR<50ml/min as this drug is renally excreted (7). Mycophenolate mofetil is another possible treatment option, at a suggested dose of 1000mg twice daily (2,17). Infliximab, a TNF-alpha inhibitor, has been used in several case studies related to steroid-resistant sarcoidosis. It is usually given in a dose of 3–5 mg per kg at week 0, 2, and 6 followed by every 6–8 weeks thereafter (2,17). Another biologic agent i.e. adalimumab is a potential treatment option but further studies are needed to prove its efficacy (2).

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The prognosis of renal sarcoidosis depends on age, race, the initial response to steroids, and the number of organ involvement. Elderly, African ethnicity, failure of response to steroids, extensive multiorgan involvement, and evidence of kidney scarring are poor prognostic indicators. ESKD is rare but if occurs, is usually due to hypercalcaemic nephropathy rather than granulomatous nephritis or glomerulonephritis (18). A large retrospective observational study consisting of 47 patients with sarcoidosis-related interstitial nephritis showed that only two patients developed ESKD requiring life-long renal replacement therapy (7). However, in the absence of steroid treatment, the decline from baseline renal function (with normal calcium levels) to ESKD (with hypercalcaemia) was seen in approximately two years (19).

There is paucity of literature regarding renal transplantation in sarcoidosis as the percentage of ESKD is low. Interestingly, a retrospective study done by French renal transplant department showed excellent patient and graft survival (94.4% of patients diagnosed with sarcoidosis) after median 42 months of follow up. Nevertheless, 27% of the patients had a relapse, and the disease recurrence occurred at a median period of 13 months. Risk factors for recurrence included primary renal disease related to sarcoidosis and a shorter delay between the last episode of sarcoidosis and renal transplantation. The authors concluded that renal transplantation may be carried out safely in transplant candidates with sarcoidosis (20).

CONCLUSION

Isolated renal sarcoidosis with acute kidney injury as an initial presentation is rare. Renal biopsy to establish the diagnosis is essential, and other diseases that can cause renal granulomatous inflammation must be ruled out. Prompt treatment is needed to avoid irreversible damage to the kidneys. Further studies are required to standardize the treatment protocol for renal sarcoidosis.

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