

Acute Interstitial Nephritis in Singapore: A Report of Five Cases

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ABSTRACT

Interstitial nephritis is an uncommon cause of acute renal failure. Reported incidence varies widely in the literature and may depend on several factors i.e. geographical location, diagnostic criteria, dietary, environmental factors and therapeutic practices. This is a retrospective study of biopsy proven interstitial nephritis in National University Hospital Singapore. We report five cases out of a total of 349 biopsies carried out during a five-year period between September 1997 and August 2002.

Four patients presented acutely with fever and or cough. In four patients, there was exposure to traditional Chinese medications and/or drugs. Renal failure in four out of the five patients progressed rapidly, three of whom required dialysis. One patient was treated with steroids. Renal function recovered in all patients with one patient who had significant residual renal impairment after one month.

Keywords: interstitial, nephritis, clinico-pathological series

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INTRODUCTION

Acute interstitial nephritis is uncommon. Histopathologically confirmed interstitial nephritis is reported to be only responsible for 2-3% of episodes of acute renal failure^(1,2). Chronic interstitial nephritis however has been reported to be the cause of unexplained renal failure with normal sized kidneys in upto 27% of cases⁽³⁾. The reported incidences of interstitial nephritis vary widely in the literature. It depends on several factors e.g. geographical distribution of the population studied, use of biopsy as diagnostic criterion and may reflect different etiologic factors in different patient groups. In addition all the etiologic factors may not have been identified as yet as in many reported cases no definite aetiology could be found⁽²⁾.

In Singapore, although interstitial nephritis has been previously reported as only accounting for 0.15% of End Stage Renal Failure (ESRF), there has been no reported description of clinical, histological features or outcome of acute interstitial nephritis. A retrospective analysis of 349 biopsies done at National University Hospital was therefore undertaken to study the incidence, clinico-pathological features and outcome of acute interstitial nephritis (AIN).

METHODS

All native renal biopsies carried out in adult patients at National University Hospital Singapore over a period of five-year (1 September 1997 to 31 August 2002) were retrospectively studied. A total of 349 biopsies were deemed adequate for diagnosis and were studied. Patients with primary glomerular pathology who also had interstitial nephritis were excluded. Five biopsies in five patients had acute interstitial nephritis giving an incidence rate of 1.4% (5 out of 349).

Aetiology

The aetiology of the interstitial nephritides was classified as follows in this study.

Drugs & Traditional Chinese Medications (TCM):

Interstitial nephritis associated with exposure to a particular drug and/or traditional medications with recovery of renal function following its withdrawal. Re-challenge with the presumed offending drug/s was not attempted.

Idiopathic: Despite a careful and thorough attempt, no specific cause could be identified as the cause of interstitial nephritis.

Clinical features

The specific features at presentation were retrospectively obtained from the clinical records. These included age at diagnosis, gender, ethnicity, the presence of hypertension (or a history of hypertension for which the patient was being treated), proteinuria (as determined by Albustix a nd/or 24-hour urine collection), serum creatinine, 24 hour

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Table I. Clinical Characteristics.

Clinical features	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5
Age in years	24	44	62	29	58
Gender, Ethnicity	F, C	M, C	F, Malay	M, C	M, C
Presenting Feature	Anaemia	Fever	Post chemotherapy neutropaenic sepsis	Fever, Cough	Cough
Proteinuria	2g/day	1.2g/day	No	Trace	Trace
Microscopic Haematuria	No	Yes	No	No	No
Eosinophilia	No	No	No	No	No
Skin Rash	No	Yes	No	No	No
Co-Morbidities	None	None	Ovarian Cancer	None	Diabetes Hypertension
Drug/Toxin Implicated	TCM	TCM NSAIDs	Cephalosporins	Not Clear	TCM
Steroid Treatment	No	No	No	Yes	No
Temporary Dialysis Needed	No	No	21 days	10 days	1 session

M: Male, F: Female, C: Chinese, TCM: Traditional Chinese Medications

creatinine clearance. Renal size and echogenicity were determined by ultrasonography.

Biopsy criteria for interstitial nephritis

Diagnostic criteria for interstitial nephritis were mononuclear cell infiltration in tubulo-interstitium not localised to the scarred areas of biopsy and absence of primary glomerular abnormality by light, immunofluorescence/peroxidase studies.

RESULTS

Patient Characteristics

Table I summarises ethnicity, age at presentation and gender of the five (three male and two female) patients. The age of the patients at diagnosis ranged from 24 to 62 years. There were four Chinese and one Malay patient. Three patients had no other disease, but one was diabetic (as well as hypertensive) and one was on treatment for neutropaenic sepsis associated with chemotherapy for ovarian cancer. Fever and cough alone or in combination were the presenting complaint in three cases. In one patient no associated factor was found. In the other four patients TCM and/or drugs were temporally associated with their clinical presentations.

Course of Renal Failure, Management and Outcome

Fig. 1 represents the severity and recovery of renal failure. One patient presented as an out patient at the peak of her renal impairment, but all the rest developed worsening renal failure after presentation. Three of the five patients required dialysis support. Of these three, one patient was treated with methylprednisolone intravenously followed by oral

prednisolone, as there was intense and active tubulo-interstitial mononuclear cell infiltration on renal biopsy. Four patients recovered renal function fully. One other patient defaulted follow-up after an initial improvement of renal function (which was documented one month after presentation).

CASE SUMMARIES

Patient 1

Clinical Presentation

A twenty-four-year-old Chinese unmarried woman, was referred for renal impairment (serum creatinine 221 $\mu\text{mol/l}$, urea 7.1 mmol/l) and anaemia, by haematologist. She had presented to her general practitioner with worsening lethargy over preceding two months and was being investigated for anaemia.

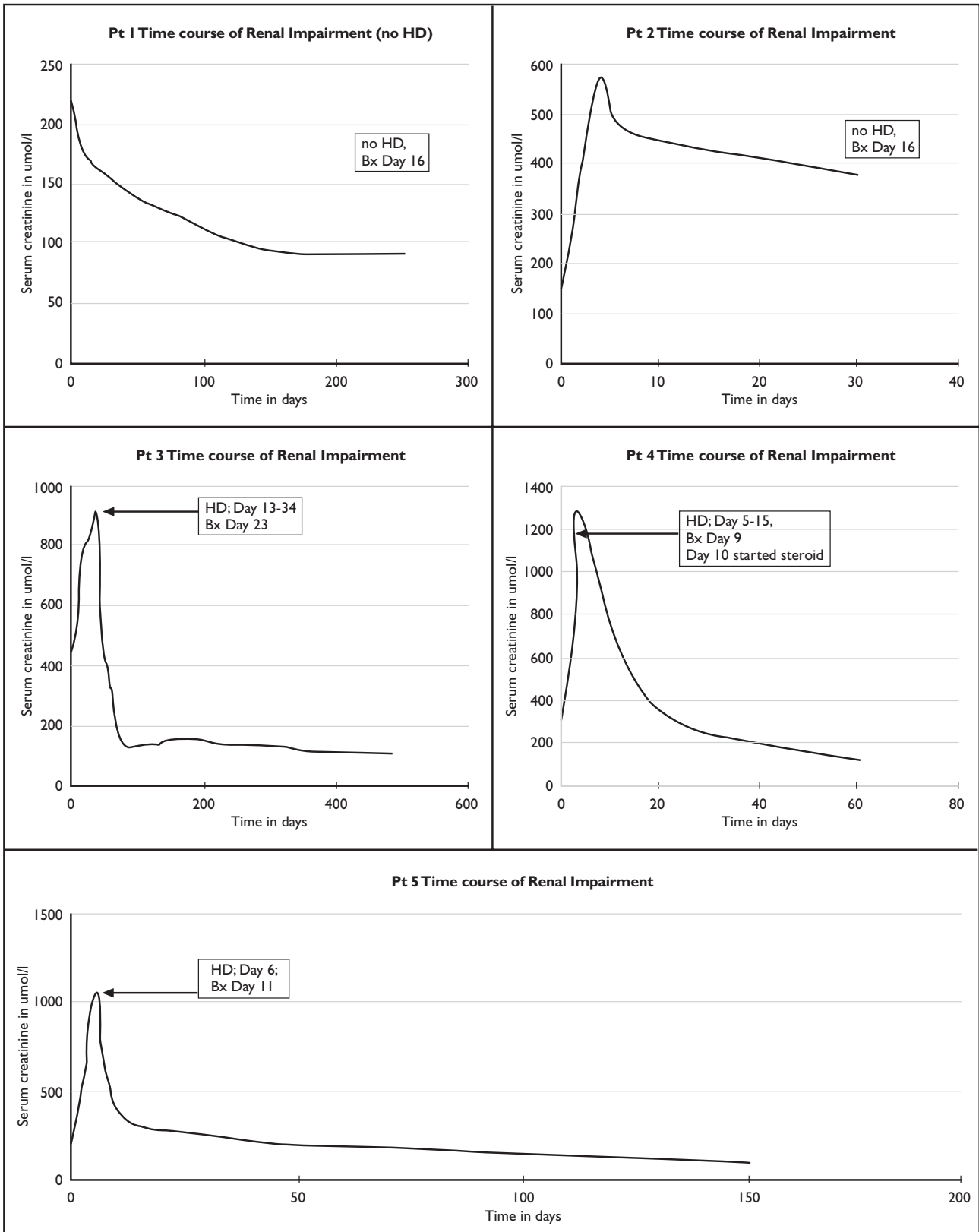
She used TCM (but no other medication) for two months for irregular menses. There was neither any evidence of blood loss, menorrhagia nor any gastrointestinal symptoms, fever, cough, weight loss, rash, joint pains, dysuria, nocturia, frothy urine, macroscopic haematuria, passage of renal stone or hearing difficulties. There was no history of diabetes or renal problems in her or her family. There were no known allergens.

On clinical examination she was pale, but not icteric. She was euvoelaemic with blood pressure of 140/80 mm of Hg. There was no pedal oedema, rash, lymphadenopathy or abdominal organo-megaly. Cardio-vascular, respiratory, and gynaecological examinations were unremarkable.

Investigations for Anaemia

Her haemoglobin was 9g/dl, with normal MCV, white cell and platelet counts. There was no eosinophilia.

Fig. 1 Time Courses, Severity and Management of Renal Impairment in all the five patients.



HD: Haemodialysis, Bx: Renal Biopsy.

Her serum B₁₂, folate, iron and ferritin, Coomb's and HAMS Tests were normal or negative; cold agglutinin was not detected in serum. Chest X-ray, liver function tests, myeloma screen, complements C₃, C₄, Anti DNA, Anti Nuclear, Anti Neutrophil Cytoplasmic (Anti

Myeloperoxidase, Proteinase 3) Antibodies were negative or normal. Bone marrow examination revealed reactive changes, a non-caseating granuloma with Langhans giant cell was identified, however acid fast bacilli, subsequent mycobacterial culture, and TB

DNA Polymerase Chain Reactions were negative. Cyto-genetic analysis of marrow was normal, 46, XX. She had no lymphadenopathy on a normal CT Scan of abdomen and pelvis.

Clinical Course of Renal Impairment

At presentation there was proteinuria of 2 g/day (but no microscopic haematuria), creatinine clearance of 38.45 ml/min, serum creatinine was 221 $\mu\text{mol/l}$, and urea was 7.1 mmol/l. Urine microscopy was unremarkable. Her kidneys were normal on ultrasound (bipolar lengths: right 10.6 cm and left 11.5 cm). Renal biopsy showed 23 glomeruli, all of which showed mild mesangial hypertrophy but no hypercellularity. Capillary walls were not thickened. There were areas of well-defined tubulitis, lymphocytic infiltration with extension into tubular lumina. There was marked diffuse inflammation with lymphocytes, plasma cells, mononuclear cells and in foci, eosinophils and polymorphs. There were two focal aggregates of histiocytes but no definite granuloma formation. Blood vessels showed no vasculitis. Immunofluorescence microscopy with anti human IgG, A, M, C₃, C₄, C1q, fibrinogen, kappa and lambda chains were negative. A diagnosis of acute interstitial nephritis was made.

Her anaemia and renal function spontaneously improved. At three weeks after presentation her serum creatinine and urea had come down to 162 $\mu\text{mol/l}$ and 4.8 mmol/l (from 221 $\mu\text{mol/l}$ and 7.1 mmol/l) respectively. Five months after withdrawal of TCM her serum creatinine and urea were 96 $\mu\text{mol/l}$ and 4.8 mmol/l respectively with 24 hour urinary protein 0.27g and creatinine clearance 73 ml/min. She attended follow up till nine months post presentation when her serum creatinine and urea recovered to 90 $\mu\text{mol/l}$ and 4.0 mmol/l respectively. Her 24-hour proteinuria was 0.15g and creatinine clearance 78 ml/min. Her urine dipstick was negative for blood, protein and microscopy showed no white/red cells or casts. Her haemoglobin was 13.8 mg/dl with normal (total as well as differential) white cell and platelet counts. She declined further bone marrow examination.

In summary this patient presented with renal impairment and anaemia five weeks after stopping usage of TCM for eight weeks. Meticulous clinical examination and extensive investigations failed to identify another cause/s for either. Both renal function and anaemia recovered with withdrawal of TCM but without any specific treatment.

Patient 2

Clinical Presentation

This was a forty-four-year-old Chinese, normotensive, non-diabetic man who was a food handler by

profession. He was admitted with a serum creatinine of 116 $\mu\text{mol/l}$. He had four-day history of abdominal pain, headache and fever up to 39°C. He also had associated, malaise, chills and dark urine but no macro or microscopic haematuria. He had no preceding cough/sputum, dysuria, or dysphagia. He had a skin rash with intramuscular penicillin injection for a skin abscess four years ago but had no other known allergy. There was no other significant past medical history.

On clinical examination he was pyrexial with temperature of 37.5°C. There was no skin rash. Blood pressure was 120/80 mm Hg. He was anicteric with suffused conjunctiva but had no neck stiffness. There was no lymphadenopathy or abdominal distension, tenderness or organomegaly. Thorough cardiovascular, respiratory and neurological examinations were unremarkable.

He had taken TCM on two days prior to admission. His general practitioner also treated him with mefenamic acid three days before as well as on the day of presentation. On admission he was treated with doxycycline, mefenamic acid was stopped.

Investigations

His blood counts were normal with no eosinophilia. There was microscopic haematuria (20 red cells per high power field), but there were no white cells (or eosinophils), crystals, casts, on repeated microscopy. Proteinuria was 1.2 g/day. Urine myoglobin, serum creatinine kinase, dengue serology IgG, IgM, leptospira culture (urine and blood), Anti HAV IgM, HbsAg, HbeAg, peripheral blood film for malaria parasite (three), C₃, C₄, Anti DNA, ANA were negative or normal. Chest X-ray was normal and renal ultrasonogram showed bipolar lengths of kidneys to be right 11.6, left 13 cm respectively with normal echogenicity. He underwent a kidney biopsy.

The biopsy showed twenty glomeruli, all of which (except one obsolescent) were normal. There were isolated areas of tubulitis. The interstitium showed moderate inflammatory cellular infiltration of plasma cells, lymphocytes, eosinophils and a few polymorphs. There was no vasculitis. There were no deposits in glomeruli on immuno-fluorescence microscopy with anti human IgG, A, M, C₃, C₄, C1q, fibrinogen, kappa and lambda light chains. A diagnosis of acute interstitial nephritis was made.

Clinical Course

His serum creatinine was 116 $\mu\text{mol/l}$ and serum urea was 5 mmol/l on admission. These peaked at serum creatinine of 568 $\mu\text{mol/l}$ and serum urea of 24 mmol/l despite adequate hydration, satisfactory urine output,

resolution of fever, on the fourth day of admission. At this time he also had a circular, transient, non-itchy macular rash on anterior abdominal wall of 3 cm diameter, that spontaneously resolved in a day. His renal function recovered spontaneously. The serum creatinine was 459 $\mu\text{mol/l}$ (urea 22 mmol/l) by the seventh day post admission. At one month after presentation his serum creatinine had improved to 376 $\mu\text{mol/l}$. He had on urine examination a trace of protein, no blood with normal urine microscopy. Subsequently he defaulted follow up.

Patient 3

Clinical Presentation

A Malay lady of 62 years presented with fever and neutropenia. She had stage 3C ovarian cystadenocarcinoma with metastatic disease in peritoneum, omentum, sigmoid and transverse colon. She underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy with colectomy (and a colostomy) as debulking procedure five months prior to presentation. Post operatively she had several cycles of carboplatin and cyclophosphamide up to two weeks before presentation. She was normotensive and non-diabetic. There was no history of consumption of TCM or NSAID.

She was pyrexial and temperature was 39°C but had no skin rash/purpuric spots, sore throat, cough with sputum, and diarrhoea. On systemic clinical examination she was euvolaemic with blood pressure of 140/80 mm of Hg. She was pale but not jaundiced. She had no abdominal organomegaly or tenderness, palpable lymph nodes in neck, axillae or groins, lung fields were clear.

Investigations on admission

She was pancytopenic on admission. There was no blood or protein on urine dipstick examination. Urine microscopy was unremarkable. Her serum creatinine was 97 $\mu\text{mol/l}$ and urea 10.3 mmol/l . Chest X-ray was normal.

Clinical Course

Intravenous ceftriaxone was started on admission and gentamicin was added two days later. In addition ceftriaxone was changed to ceftazidime in view of persistence of fever and negative cultures. She remained neutropaenic, thrombocytopenic and pyrexial. She was supported with G-CSF, blood and platelet transfusions. Her blood, urine and sputum cultures remained negative. Her serum creatinine rose to 116 $\mu\text{mol/l}$ nine days after presentation. Her blood counts recovered and fever resolved. On tenth day of presentation her serum creatinine went up to 186 $\mu\text{mol/l}$ and she underwent a CT scan

of abdomen and pelvis with contrast. Two days later her urine output declined. Ultrasound scan showed normal sized unobstructed kidneys (right 10.7 and left 10.8 cm in bipolar length). She became oligo-anuric and required haemodialysis from day 13 to day 34. On day 14 she was dyspnoeic and a chest X-ray revealed a significant right apical pneumothorax which required a chest tube insertion.

As her renal function did not recover (she remained haemodialysis dependent), she underwent a renal biopsy on day 23. There were 30 glomeruli. One was sclerosed, with the rest having mild mesangial thickening but no hypercellularity or capillary luminal thrombosis. There was diffuse moderate infiltration with chronic inflammatory cells i.e. lymphocytes, plasma cells, eosinophils and some polymorphs in foci. The diagnosis was acute tubulointerstitial nephritis. From the 30th day her urine output slowly improved. The serum creatinine after a year was 112 $\mu\text{mol/l}$. Urine examination was negative for blood and protein with no eosinophils or white/red cells or casts on microscopy.

Patient 4

Clinical Presentation

A twenty-nine-year-old Chinese man (shipyard worker) was admitted with cough, fever (temperature was 39°C) with chills, rigor and myalgia for three days. He was normotensive and non-diabetic. He did not take any medication or herbs. He had no known allergens. There was no preceding history of foreign travel, rash, joint pains, and weight loss, diabetes, macroscopic haematuria, renal stones, hearing difficulty, or family history of kidney disease.

On clinical examination he was febrile, normotensive (blood pressure 120/70 mmHg), and euvolaemic. There was no rash, lymphadenopathy, abdominal organomegaly, distension or tenderness. Examination of cardiovascular system and lungs was unremarkable.

Investigations

The blood counts were normal and there was no eosinophilia (absolute or differential). His C reactive protein and serum creatinine kinase enzyme levels were normal. There was a trace of protein but no blood in urine dipstick examination. Urine microscopy was unremarkable. His chest X-ray, ultrasound scan of kidneys and SLE serology were normal. His sputum, urine and blood cultures were sterile. There was no acid fast bacilli in sputum. Screening for atypical pneumonia, dengue and leptospira were negative. Peripheral smear for malaria parasites on three occasions were negative.

Clinical Course

His serum creatinine on admission was 227 $\mu\text{mol/l}$. His renal function rapidly deteriorated. Serum creatinine rose to 614 $\mu\text{mol/l}$ and serum urea to 13.6 mmol/l, 835 $\mu\text{mol/l}$ (urea 16.6 mmol/l), 1278 $\mu\text{mol/l}$ (urea 22.6 mmol/l) on first, second, third and fourth days respectively post admission. He became oligo-anuric, and was dialysis dependent by the fifth day. He underwent a kidney biopsy on day 9. This revealed 10 normal glomeruli, with no evidence of vasculitis. The tubulo-interstitium however showed dense mononuclear lympho-plasmacytic infiltrate with scattered eosinophils, interstitial nephritis with intense mononuclear cell infiltrate. There was associated tubular damage with vacuolisation, flattening and thinning of the epithelium. Immuno-fluorescence staining with IgG, M, A, C1q, C₃ and fibrinogen were negative. The diagnosis was acute interstitial nephritis.

Treatment

He was treated with intravenous methyl prednisolone 1 g daily for two days followed by reducing doses of oral prednisolone, starting at 1 mg/kg body weight per day. He remained dialysis dependent till day 15. His renal function recovered thereafter i.e. serum creatinine improved to 373 $\mu\text{mol/l}$ (urea 19.3 mmol/l) on day 19. At day 60 his serum creatinine was 114 $\mu\text{mol/l}$, and he was on a tapering dose of oral prednisolone. Subsequently he left Singapore and was lost to follow up.

Patient 5*Clinical Presentation*

A 58-year-old Chinese man was admitted to another hospital with a three day history of dry cough and one day of diarrhoea and vomiting. He took TCM for four days prior to admission. He had non-insulin dependent diabetes mellitus (no retinopathy, neuropathy or history of limb claudication) treated with tolbutamide and hypertension treated with atenolol. Both conditions had been present for 10 years. He took no other medications or NSAIDs. He had no known allergies. He had not eaten out of home for the preceding five days and no other member of the family of four was affected. He had no fever, chills, sputum production, haemoptysis or dysuria. He had never passed blood or stone in urine. There was no family history of kidney diseases.

Investigation

His blood counts were normal and he had no eosinophilia. There was a trace of protein but no blood in urine. Repeated urine microscopy showed no eosinophils, white, red cells, casts, or crystals.

Serum creatinine kinase, chest X-ray, ultrasound scan of kidneys were reported normal. Microscopy of his stool showed no pathogen. The urine culture was sterile and leptospira did not grow in blood and urine cultures. Serology rickettsial, HBsAg, and anti HCV were negative.

Clinical Course

His serum creatinine on admission was 192 $\mu\text{mol/l}$. Following admission his serum creatinine rose with a fall in urine output. By days 2, 3 and 6 his serum creatinine and urea were creatinine 595 $\mu\text{mol/l}$, urea 19.6 mmol/l; creatinine 760 $\mu\text{mol/l}$, urea 21.5 mmol/l; creatinine 1036 $\mu\text{mol/l}$, urea 26.3 mmol/l respectively. He was transferred to National University Hospital, Singapore for haemodialysis. Following stabilisation of his clinical condition he underwent a renal biopsy on day 11. Glomeruli (total five in the biopsy) were normal by light and immunofluorescence microscopy (i.e. immune negative for IgG, M, C₃). There was vascular sclerosis of mild to moderate severity consistent with his hypertension. There was interstitial oedema and aggregate of inflammatory cells within the interstitium. The diagnosis was acute interstitial nephritis.

After Day 8, his renal function and urine output recovered. He was discharged on Day 14 with a improving renal function i.e. falling creatinine (307 $\mu\text{mol/l}$ and urea 21 mmol/l). His renal function further recovered and after five months his serum creatinine was 82 $\mu\text{mol/l}$, 24 hour urinary protein 0.08 g with creatinine clearance was 65.54 ml/min. His blood counts, urine dipstix and microscopy were normal.

DISCUSSION**Aetiology**

In 1898 Councilman first described interstitial nephritis as a post-infectious acute inflammatory renal disease (post mortem) associated with diphtheria and scarlet fever, with mononuclear cellular infiltrate and fluid exudate within renal interstitium⁽⁴⁾. Over the last century several other [Table II] etiological associates have been identified, such as (1) bacterial: diphtheria, streptococci, pneumococci, brucella, legionella, and histoplasma⁽⁵⁾ salmonella, campylobacter, yersinia, leptospira, syphilis and tuberculosis, (2) viral: dengue, Epstein-Barr, measles, cytomegalovirus, HIV, Hantavirus, and in immunosuppressed individuals polyoma virus, as well as (3) other organisms like toxoplasma, rickettsia and mycoplasma.

A number of systemic diseases e.g. SLE, Sjogren's syndrome, primary biliary cirrhosis, essential

Table II. Associations with interstitial nephritis.

1. Bacteria	Diphtheria, Streptococcus, Pneumococcus, Brucella, Legionella, Tuberculosis, Salmonella, Campylobacter, Yersinia, Leptospira, Syphilis	
2. Viral	Epstein-Barr, Dengue, Measles, Cytomegalovirus, Hantavirus, HIV, Polyoma,	
3. Other infectious agents	Toxoplasma, Rickettsia, Mycoplasma	
4. Drugs and toxins	Antibiotic	Penicillins, Cephalosporins, Sulfonamides, Rifampicin, Tetracycline, Isoniazide, Ciprofloxacin
	Anticonvulsant	Carbamazepine, Phenytoin, Phenobarbitone,
	Diuretic	Furosemide, Thiazides, Ethacrynic Acid
	H ₂ Antagonist	Cimetidine
	Hypouricaemic	Allopurinol, Sulphinpyrazone
	NSAIDs	All
	Others	Ergotamine
	Toxins and Hallucinogens	Copper Sulfate, Aristolochia (Chinese Herbs), Ochratoxin, Crack Cocaine

Table III. Incidence of Interstitial nephritis (Biopsy proven) and Outcome.

Study	Single centre retrospective study from	Total patients or biopsies	Interstitial nephritis incidence	Reversibility of renal function
Ball S et al 1997 ⁽²¹⁾	West London 1991 to 1993	394	30 (7.6%)	8 on RRT
Schwarz A et al 2000 ⁽²²⁾	Germany 1968 to 1997	1068	Total 6.5%, (85% drug induced)	Permanent in 31%, (36% in drug induced)
Chang CH et al 2001 ⁽¹⁴⁾	Taiwan 1994 to 1998	20 patients	All Chinese herb associated	15 on RRT, in 3 months
Present study	Singapore 1997 to 2002	349	5 (1.4%)	All, definite improvement. None on RRT

RRT: Renal Replacement Therapy

cryoglobulinaemia and other vasculitides have been associated with interstitial nephritis. Tubulo-interstitial nephritis in association with anterior uveitis (TINU) in adolescent females with elevated serum IgG was identified in 1975⁽⁶⁾. An association with Epstein-Barr virus has also been reported⁽⁷⁾.

Drugs have also been implicated as possible aetiological agents. In the UK MRC register, a drug was indicated as a possible aetiological agent in 58% of cases of isolated interstitial nephritis⁽⁸⁾. Methicillin may cause nephritis in up to 17% of treated patients⁽⁹⁾. Non steroidal anti-inflammatory drugs (NSAID)^(10,11) and ergotamine are reported to cause interstitial nephritis⁽¹²⁾.

A number of toxins have also been identified as causative agents for interstitial nephritis. Ongoing interstitial nephritis leading to end-stage renal failure has been reported with aristolochia associated nephropathy⁽¹³⁾. In a study from Taiwan, Chinese herbs were implicated in a series of biopsy proven interstitial nephritis⁽¹⁴⁾.

Crack cocaine has been reported to be associated with acute interstitial nephritis⁽¹⁵⁾ and in Tunisia

(Northern Africa) Ochratoxin A has been detected in high amounts in patients (12 to 26% of total chronic renal failure patients) with chronic interstitial nephropathy (similar to Balkan endemic nephropathy) of unknown aetiology⁽¹⁶⁾.

Incidence and Prevalence

Interstitial nephritis has been observed in 2%⁽¹⁾, 3%⁽²⁾ and 5.3% (in the elderly)⁽¹⁷⁾ of unselected renal biopsies. When biopsy was performed for diagnosis of acute renal failure, the incidence of interstitial nephritis was higher, accounting for 3%^(18,19) to 15%⁽²⁰⁾ cases. However the frequency of interstitial nephritis has been reported as high as 27% when the biopsy was performed for unexplained acute renal failure with normal sized kidneys⁽³⁾.

A definite causative factor for interstitial nephritis is not always recognisable and is therefore termed idiopathic interstitial nephritis. Incidence of idiopathic interstitial nephritis varies according to the study and the ethnic origin of the subjects studied. In a study of 394 biopsies (from west London with a large population of patients from Indo-Asian origin),

30 cases of interstitial nephritis were identified (an incidence of 7.6%) of whom 17 were originally from India. In 15 of these Indian patients no aetiology could be established⁽²¹⁾. Interestingly none of the five cases reported in the current study was of Indian origin.

In a retrospective review from Hanover, Germany, of 1068 renal biopsies carried out over 20 years (1968 to 1997), acute interstitial nephritis was found in 6.5% of all biopsies. The AIN was infection associated in 10%, idiopathic in 4%, and drug associated in 85% of the cases⁽²²⁾.

Reversibility of Renal Function

In the same large retrospective study⁽²²⁾ by Schwarz et al, from Germany, reversibility of renal insufficiency was reported in 69%. Of the remaining 31%, 12% partially reversible, 19% were irreversible. Infection-induced and idiopathic types of AIN were always reversible. Drug associated AIN caused permanent renal insufficiency in 36% but in NSAID induced cases this happened in 56%. In drug associated cases, intake of the suspected drug for more than a month prior to diagnosis, caused permanent renal insufficiency in 88%.

A multivariate analysis found the several features predictive of permanent renal insufficiency. These were 1) tubular atrophy on histology; 2) chronic use of analgesics and/or NSAIDs; 3) oliguria or anuria as an acute presenting symptom; 4) pronounced interstitial cell infiltration in histology; 5) reduced renal size on imaging. Renal histological features had the highest predictive value for irreversibility⁽²²⁾.

In the present study (in 349 biopsies over five years), there were five cases of interstitial nephritis, giving an incidence of 1.4% of unselected renal biopsies. Three of the five patients had consumed traditional Chinese medications (in one patient NSAID was also used). One patient had sepsis with exposure with cephalosporins and gentamicin. Drugs therefore were implicated in four out of five of the patients in this study.

The clinical features of all the patients were protean and non-specific. Urine examination was generally not helpful. Four patients had proteinuria. Two patients each had a trace and moderate (1 to 2 g/day) proteinuria. Microscopic haematuria was present in only one patient at presentation. None had eosinophilia or eosinophiluria.

None of the patients had any known allergens except for one patient who was known to be allergic to penicillin. Only one patient (Pt 2) developed a transient non-itchy macular 3 cm rash on anterior abdominal wall that spontaneously resolved in a day.

Role of Steroid Therapy in Interstitial Nephritis

Recovery is usual in most cases of acute interstitial nephritis even in presence of oliguria or dialysis dependency⁽¹⁾. Discontinuation of possible offending agent, and/or treatment of infection (if suspected to be the cause), as well as associated systemic disorders alone are usually sufficient. Therefore the role of steroids in this setting is controversial. All the reported cases of steroid therapy have however been retrospective and uncontrolled^(1,2). Results have varied, in methicillin related cases, prednisolone (60 mg/day) for ten days was reported to shorten the period of oliguria⁽²³⁾. Intravenous methyl-prednisolone treatment was associated with an increase in urine output and fall in serum creatinine within 72 hours when compared to the untreated group. Patient groups were not randomised or controlled for severity and aetiology⁽¹⁹⁾.

In a review⁽²⁾ by Buysen et al 1990, of 27 cases of mixed aetiology (drug-related in 15, infection-related in nine, and idiopathic in three), renal function had spontaneously returned to normal in 10, improved in seven, and remained unchanged in 10 by a mean of 10 days (range 5-20). The latter group were given steroids (intravenous methyl-prednisolone 1 g/day for three days or oral prednisolone 40-60 mg/day for three to four weeks) and showed prompt improvement in renal function.

Thus on the basis of current literature, in the absence of contraindications, in patients with acute interstitial nephritis, the use of short course of moderately high doses of oral prednisolone (40 to 60 mg/day) for one week with a rapid taper may be justifiable. It may however be prudent to delay this by 10 days to see if spontaneous recovery occurs. This was the reasoning behind treating one of our patients [#4] with steroids.

Factors that influence prognosis/progression

Acute interstitial nephritis usually presents with deterioration in renal function over days or weeks with potential reversibility following withdrawal of the offending agent. This is irrespective of the severity of renal failure and/or dialysis requirement in most cases. The infection-induced and idiopathic types of acute interstitial nephritis are associated with good prognosis, whereas NSAIDs and drug-related acute interstitial nephritis, specially with prolonged exposure have a high incidence of permanent renal insufficiency⁽¹¹⁾.

Significant features separating the permanent from the reversible renal insufficiency is tubular atrophy in histology, pronounced interstitial cell infiltration and renal shrinkage in imaging. Renal histology had the highest predictive value⁽²²⁾.

SUMMARY AND CONCLUSION

In summary, this study reports five patients with interstitial nephritis with giving an incidence of 1.4% of unselected biopsies (total 349) done over five years. The patients in this study demonstrate the following features.

1. Drugs (and toxins) are common causes of acute interstitial nephritis presenting as acute deterioration of renal function.
2. The severity of renal impairment varies. This was not predictive of recovery of renal function.
3. Withdrawal of offending agent with supportive care leads to recovery of renal function in most cases of interstitial nephritis even without steroid therapy.

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