Clinical Approach to Rapidly Progressive Renal Failure

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Abstract
Rapidly progressive renal failure (RPRF) is an initial clinical diagnosis in patients who present with progressive renal impairment of short duration. The underlying etiology may be a primary renal disease or a systemic disorder. Important differential diagnoses include vasculitis (systemic or renal-limited), systemic lupus erythematosus, multiple myeloma, thrombotic microangiopathy and acute interstitial nephritis. Good history taking, clinical examination and relevant investigations including serology and ultimately kidney biopsy are helpful in clinching the diagnosis. Early definitive diagnosis of RPRF is essential to reverse the otherwise relentless progression to end-stage kidney disease.

Concept of Rapidly Progressive Renal Failure
In clinical medicine physicians encounter patients who present with progressive renal impairment of seemingly unknown etiology. The duration of disease is brief or may even be undefined. These patients are neither Acute Kidney Injury (previously called acute renal failure) nor Chronic Kidney Disease (previously called chronic renal failure). The initial clinical diagnosis of these cases may be called Rapidly Progressive Renal Failure (RPRF), which may be defined as progressive renal impairment over a period of few weeks. On ultrasonography of the kidneys, patients with RPRF have normal sized kidneys, while the presence of small contracted echogenic kidneys establishes the diagnosis of CKD. Actually RPRF encompasses a heterogeneous group of clinical syndromes. The renal histopathology shows lesions affecting any or a combination of the three traditional renal compartments: glomerular, tubulointerstitial or vascular. The diseases causing RPRF are listed in Table 1. Since a wide variety of different diseases may present with a similar clinical picture, it is essential to properly work-up cases of RPRF so that the exact diagnosis is established. Time is a valuable factor since if the appropriate treatment is not initiated, then the patient may progress to irreversible end-stage renal disease (ESRD) needing life-long renal replacement therapy. RPRF may in fact be considered as ‘Renal Emergency’. Hence the role of the physician, who sees the patients in the initial stages is vital to ensure optimal management of RPRF. The traditional approach to a patient namely history, physical examination and appropriate investigations all play a vital role in the diagnostic work-up. Ultimately kidney biopsy is required in most patients.

History
Detailed and appropriate history taking is essential both to make the initial diagnosis of RPRF (by excluding CKD and AKI), and also to arrive at the cause of RPRF. History of hematuria, hemoptysis, longstanding asthma or petechiae is suggestive of vasculitis, while arthralgia, oral ulcers or photosensitivity indicates presence of lupus. In the middle aged and elderly it is essential to ask for history of backache or bone pains, since multiple myeloma sometimes presents with renal impairment. While evaluating a case of suspected RPRF, it is essential to diligently go through the medical records of the patient. It is not unusual to find documentation of abnormal urine examination and / or impaired renal function of which the patient is unaware of. Long-standing history of diabetes and hypertension makes it likely that the patient has diabetic or hypertensive nephropathy.

Physical Examination
Since anemia is one of the important features of CKD, absence of pallor is one of the signs that may suggest RPRF. In general, patients with RPRF have normal BP. However hypertension is a feature in patients with underlying thrombotic microangiopathy (TMA) and renal artery stenosis. Finding of oral ulcer or butterfly rash is indicative of lupus, while skin petechiae may indicate lupus or vasculitis.

Investigations
The sine qua non of RPRF is impaired renal functions in a patient with short history (2 weeks – 3 months). The most important investigation which suggests the diagnosis of RPRF is the presence of normal sized kidneys on ultrasonographic examination of the abdomen. Significant dilatation of the pelvi-calyceal system and the ureters suggests obstruction to the urinary tracts. Urine examination by a trained pathologist is of great help. Active urinary sediment (proteinuria, dysmorphic RBCs and RBC casts) suggests proliferative glomerulonephritis, while hematuria with isomorphic RBCs is indicative of acute interstitial nephritis. Table 2 gives a list of non-invasive investigations which are useful to arrive at the cause of RPRF. Appropriate investigations need to be sent depending on the history and clinical findings.

Role of Kidney Biopsy
As mentioned earlier, most cases of RPRF need a renal biopsy either to make the correct diagnosis or to understand the chronicity of the disease process. The various histological diagnoses, which may be seen in patients with RPRF are as follows:

Crescentic Glomerulonephritis
One of the most important causes of RPRF is Rapidly Progressive Glomerulonephritis (RPGN). RPGN is a clinic-
Table 1: Diagnostic Causes of Rapidly Progressive Renal Failure

1. Primary Renal Diseases
   a. Glomerular diseases
      i. Renal limited Vasculitis: Microscopic polyangiitis, ANCA neg. pauci-immune GN, Goodpasture’s disease
      ii. Post-infective crescentic glomerulonephritis
      iii. Idiopathic Collapsing glomerulopathy
      iv. IgA nephropathy, Membrano-proliferative glomerulonephritis
      v. Fibrillary glomerulonephritis
   b. Tubulo-interstitial diseases
      i. Acute interstitial nephritis
      ii. Acute tubular necrosis
   c. Vascular diseases
      i. Atheromatous and thrombo-embolic renovascular disease
      ii. Bilateral renal vein thrombosis

2. Systemic diseases affecting the kidney
   a. Systemic vasculitis
      i. Wegener’s granulomatosis
      ii. Churg-Strauss Syndrome
      iii. Goodpasture’s syndrome
      iv. Henoch-Schonlein Purpura
      v. Cryoglobulinemia
      vi. Drugs- hydralazine, allopurinol, rifampicin, propylthiouracil, carbimazole
      vii. Rheumatoid vasculitis, paraneoplastic vasculitis
   b. Multiple myeloma
   c. Systemic Lupus Erythematosus
      i. Class IV lupus nephritis
      ii. Antiphospholipid antibody syndrome
   d. Thrombotic microangiopathy
      i. HUS / TTP
      ii. Malignant hypertension
      iii. Systemic sclerosis
   e. Infections
      i. Infective endocarditis
      ii. Occult viscera sepsis
      iii. Hepatitis C
   f. Sarcoïdosis
   g. Obstructive nephropathy
      i. Retroperitoneal fibrosis
      ii. Pelvic malignancy eg carcinoma cervix

pathological syndrome; and is characterised clinically by rapid loss of renal function, and pathologically by extensive crescents often with necrosis of the glomerular tuft. A crescent forms as a result of the proliferation of the glomerular epithelial cells resulting in compression of the glomerular tuft (Figure 1). Crescentic glomerulonephritis occurs commonly in the various forms of vasculitis (both primary renal and systemic); and occasionally in post-infective glomerulonephritis, lupus nephritis, IgA nephropathy and membrano-proliferative glomerulonephritis. Clinical features of RPGN may consist of cola-coloured urine, generalized non-specific constitutional symptoms or a flu-like syndrome. Blood pressure is normal or only slightly raised. Purpura may be present. Signs and symptoms of the underlying disease may be present, and provide a clue to the diagnosis. A small but significant percentage of patients may be asymptomatic. The two important tests, which help in the differential diagnosis of RPGN are serum Anti-neutrophilic Cytoplasmatic antibody (ANCA), which is of two types viz. p-ANCA (directed against myeloperoxidase) and

Table 2: Investigations which give a clue to the diagnosis of RPRF

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucocytosis</td>
<td>Sepsis, Vasculitis, Thrombo-embolic disease</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>Churg-Strauss Syndrome, AIN</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>HUS / TTP</td>
</tr>
<tr>
<td>Peripheral smear with fragmented RBCs</td>
<td>TMA</td>
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<tr>
<td>Urine dipstick protein negative to 1+ only, but 24 hr collection: total proteins disproportionately high</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Urine showing active sediments</td>
<td>Vasculitis, Lupus nephritis, Dysmorphic RBCs RBC casts</td>
</tr>
<tr>
<td>Proteinuria (sub-nephrotic)</td>
<td>AIN</td>
</tr>
<tr>
<td>Urine showing nephrotic range proteinuria</td>
<td>Collapsing / Fibrillary glomerulonephritis</td>
</tr>
<tr>
<td>Serum: Hypercalcemia</td>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td>Serum: Hypercalcemia, hyperuricemia, raised globulins Serum LDH raised</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Serological tests positive for:</td>
<td>TMA, Thrombo-embolic disease</td>
</tr>
<tr>
<td>ANA</td>
<td>Lupus Nephritis</td>
</tr>
<tr>
<td>C3, C4 and CH50 reduced</td>
<td>Lupus nephritis, Cryoglobulinemia</td>
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<tr>
<td>C3 and CH50 reduced, C4 normal</td>
<td>Post-streptococcal glomerulonephritis</td>
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<tr>
<td>Antiphospholipid antibodies against antigens: anticardiolipin, anti-ß2glycoprotein</td>
<td>Antiphospholipid antibody syndrome</td>
</tr>
<tr>
<td>ANCA</td>
<td>Vasculitis (Pauci-immune glomerulonephritis)</td>
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<tr>
<td>Anti-GBM antibodies</td>
<td>Goodpasture’s Syndrome / Disease</td>
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<tr>
<td>Anti-Streptolysin O (ASLO)</td>
<td>Post Streptococcal</td>
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<tr>
<td>Anti-DNAase</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>Rheumatoid vasculitis</td>
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<tr>
<td>Anti-Scl 70</td>
<td>Systemic sclerosis</td>
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<tr>
<td>Cryoglobulins</td>
<td>Cryoglobulinemia</td>
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<tr>
<td>Anti Hepatitis C antibodies</td>
<td>MPGN</td>
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<tr>
<td>HIV antibodies</td>
<td>Collapsing Glomerulopathy, TMA</td>
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<tr>
<td>HBsAg</td>
<td>MPGN, vasculitis</td>
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<tr>
<td>ADAMTS 13 deficiency</td>
<td>TTP</td>
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<tr>
<td>Serum protein electrophoresis showing ‘M’ spike</td>
<td>Multiple myeloma</td>
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<tr>
<td>Urine protein electrophoresis for κ &amp; λ chains</td>
<td></td>
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<tr>
<td>X-ray Chest showing cavities</td>
<td>Wegener’s Syndrome</td>
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<tr>
<td>USG kidneys:</td>
<td>RPRF /AKI</td>
</tr>
<tr>
<td>Normal size</td>
<td>Chronic kidney disease</td>
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<tr>
<td>Small size</td>
<td>Retroperitoneal fibrosis</td>
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<tr>
<td>CT scan abdomen</td>
<td>Multiple myeloma</td>
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<tr>
<td>Bone marrow examination</td>
<td></td>
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<tr>
<td>Doppler/ CT Angio / MR Angiography</td>
<td>Renal artery stenosis</td>
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c-ANCA (directed against PR3); and the immunofluorescence (IF) examination of the kidney biopsy. Figure 2 depicts an algorithm using ANCA and IF in patients with crescentic glomerulonephritis to arrive at the exact diagnosis.

6,7 A large majority of cases of crescentic glomerulonephritis are pauci-immune. 3 Anti-GBM disease is quite rare and accounts for about 5% of all cases of crescentic glomerulonephritis. 7

Lupus Nephritis

Occasionally lupus presents initially only with renal involvement. Lupus nephritis is diagnosed on kidney biopsy along with evidence of positive serology. Immunofluorescence examination showing deposition of IgG, IgM, IgA, C3 and fibrinogen (full-hose deposition) is highly suggestive of lupus nephritis. The classification of lupus nephritis into 5 classes is based primarily on the glomerular involvement. 8 However lupus nephritis also involves the interstitium and renal blood vessels in varying degrees. 9 RPRF occurs mainly in two groups of patients:

1. Lupus nephritis Class IV

2. Thrombotic microangiopathy as a result of lupus nephritis

This is associated with the presence of antiphospholipid antibodies

These entities can only be diagnosed by kidney biopsy. Hence it is desirable to perform kidney biopsy in all lupus patients with active urinary sediments, so that these entities can be diagnosed early. Appropriate immunosuppression can help in achieving renal recovery. Delay in diagnosis results in irreversible loss of renal function.

Thrombotic Microangiopathy

Thrombotic microangiopathy affects arterioles and glomerular capillaries. The histologic lesions of arteriolar type of TMA consist of myointimal proliferation, reduplication of the lamina elastica and intraluminal platelet thrombi resulting in partial or total obstruction of the vessel lumen (Figure 3). The glomeruli, when affected, show thrombi in the capillary loops and mesangiolysis. The important causes of TMA include Shiga-toxin induced HUS, TTP due to ADAMTS13 deficiency, pregnancy, antiphospholipid antibody syndrome, systemic sclerosis, malignant hypertension and certain drugs. 10 TMA is suspected on the basis of history, thrombocytopenia and evidence of microangiopathic hemolytic anemia (peripheral smear showing fragmented RBCs and raised serum LDH).

Multiple Myeloma

Occasionally multiple myeloma presents to the clinician primarily as RPRF without the classical symptoms. Hence a high index of suspicion is needed especially if investigations reveal hypercalcemia in the presence of renal impairment, hyperuricemia and raised serum globulins. The diagnosis is made by serum and urine protein electrophoresis, and bone marrow examination.

Early diagnosis and institution of treatment may reverse the renal failure.

Thrombo-embolic Disease

Atheromatous renal artery stenosis and cholesterol embolisation to the kidney are often associated, and are a cause of ischemic renal disease leading to subacute renal failure.
Thrombo-embolic renal disease occurs as a result of cholesterol embolism after manipulation of the aorta: angiography, angioplasty and vascular surgery. Occasionally it may occur spontaneously in patients with extensive atherosclerosis. On kidney biopsy cholesterol clefts are seen in medium sized vessels with giant cell reaction and re-canalisation.11

Acute Interstitial Nephritis

The clinical presentation of acute interstitial nephritis (AIN) may be like RPRF or sometimes even AKI. About half of all cases of AIN are caused by drugs. The other causes include various infections, malignancies and sarcoidosis.12

Acute Tubular Necrosis

Although acute tubular necrosis (ATN) usually presents abruptly, on rare occasions renal biopsy of a suspected RPRF case reveals ATN.

Distribution of the Various Histological Entities

A recent retrospective study from the Spanish Registry of patients with RPRF, in whom kidney biopsy was done, has shown that crescentic glomerulonephritis accounted for 33% cases, AIN 11%, IgA 9%, ATN 5%, and lupus nephritis, PIGN, myeloma kidney and TMA approx 3% each.13 In another similar study in elderly patients with RPRF, crescentic GN accounted for 71% cases of RPRF, and AIN 17%.14

Treatment of RPRF

Since the causes of RPRF are very heterogeneous, the treatment will also be varied. The details of specific treatment modalities for the various causes of RPRF are beyond the purview of this review. Vasculitis and lupus nephritis need prompt immunosuppression, sometimes with plasmapheresis; while multiple myeloma needs appropriate chemotherapy. Of the various vasculitic syndromes HSP has a relatively good renal prognosis as compared to the ANCA associated vasculitis.15 Treatment related infection is a major cause of morbidity and mortality especially in the developing countries. Acute interstitial nephritis usually responds to withdrawal of the offending medication along with a short course of oral steroids. The treatment of TMA necessitates aggressive BP control (with ACE inhibitors if required), plasmapheresis and removing the cause if possible. Interferon a therapy is beneficial in Hepatitis C mediated cryoglobulinemia and renal involvement. Collapsing glomerulopathy and fibrillar glomerulonephritis are treated with steroids, but the response to treatment is usually unsatisfactory.7 Atheromatous renal artery stenosis resulting in ischemic renal disease needs renal re-vascularisation.16 Bypassing the obstruction with internal ureteric stent/s or percutaneous nephrostomy/ies are indicated if there is obstructive nephropathy.

Conclusion

Rapidly Progressive Renal Failure is a useful initial clinical diagnosis for patients who present with progressive renal impairment of short duration. It is not the final definitive diagnosis and needs prompt evaluation including good history, physical examination and appropriate investigations. A battery of serology tests and finally kidney biopsy (in most cases) helps in establishing the definitive diagnosis. Appropriate aggressive treatment can help in preventing progression to end-stage renal disease.

Acknowledgement

Dr. AK Dinda for providing the photomicrographs (Figs. 1 and 3)

References

ALCAPA in an Adolescent Girl

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A 15 year-old girl with fatigue was referred for Echocardiogram. She had a grade 4/6 ejection systolic murmur in pulmonary area and S3 gallop. ECG – Fig. 1, showed q in leads 1, aVL and ST squaring in leads V4 to V6. Chest X-ray revealed dilated main pulmonary

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Received: 04.09.2009; Revised: 02.11.2009; Accepted: 09.11.2009
artery (MPA). In the long axis parasternal view of echocardiogram, a dilated right coronary artery (RCA) measuring 10mm was noted – Fig. 2. The IVS was hypokinetic and LV function was depressed. In the short axis parasternal ductus view a narrow vessel with turbulent flow draining into MPA and end –on- view of some vessels were noted – Fig 3 and 4. Anomalous Left Coronary Artery arising from Pulmonary Artery - ALCAPA was suspected. A 3- minute walk caused chest discomfort to the patient and an ECG taken immediately showed T inversion in the leads 1, aVL and V4 to V6 i.e. features of inducible ischaemia. The patient was referred to a tertiary cardiac center where she underwent coronary angiogram that confirmed the origin of left main coronary artery (LMCA) from pulmonary artery. The RCA was dilated and tortuous with collaterals that drained into the left coronary system and then flowed into MPA – Figs. 5, 6 and 7. At surgery, the dilated RCA arising from aorta and the narrow LMCA arising from the lateral aspect of MPA were seen. The pulmonary artery was opened longitudinally and the coronary ostium was closed with a pericardial patch. Coronary steal into the pulmonary artery ceased and the patient recovered well. At six month follow-up, her effort tolerance is normal and LV function has improved.

ALCAPA is a very rare diagnosis in adults, its incidence being 1 in 300,000 live births and 0.2-0.5% of all congenital heart diseases. More than 90% of the children born with ALCAPA die within the 1st year of life. Those who survive depend on blood flow through the collaterals between the right and left coronary systems. But the inadequate myocardial blood flow, due to “steal” into the low pressure pulmonary artery, leads to ischaemic dilated cardiomyopathy and makes them prone to sudden cardiac death from ventricular arrhythmia. Less than 10% of the adults with ALCAPA survive beyond two decades. In this 15-year old girl with fatigue and a systolic murmur the ECG evidence of ischaemia and echocardiographic clues to abnormal coronary artery system helped us to make the rare diagnosis of ALCAPA and it could be surgically corrected.

Acknowledgement
The authors are grateful to Dr. B. Ray, General Manager, Medical Services of Tata Main Hospital, Jamshedpur and the authorities of RNTIICS, Kolkata for their permission to publish this case.

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