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Contents

Original Articles

Case Reports

Urology, Nephrology and Andrology International

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Original Article

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Renal Tubular Acidosis in Sjögren's Syndrome: A Case Series

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Abstract

Background: The exact frequency of Renal Tubular Acidosis (RTA) in Sjögren's syndrome is unknown. The aim was to study the clinical features and outcome of RTA in Sjögren's syndrome. *Methods:* The present study is a incidental cohort of consecutive case series of patients who presented with a history suggestive of RTA and Sjögren's syndrome from January 2014 to May 2016. The diagnosis of RTA was by Arterial Blood Gases analysis(ABG). The diagnosis of Sjögren's syndrome was according to the American-European classification system [modified by Tzioufas and Voulgarelis: Best Pract Res Clin Rheumatol 2007; 21: 989-1010]. *Results:* The total number of Sjögren's patients diagnosed during this period was 113. RTA occurred in 9.7% (11 of 113) of Sjögren's patients. The important symptoms were oral and ocular in 7 of 11 and laboratory parameters were mean serum pH 7.12±0.12, mean serum bicarbonate, 13.03 ± 2 mmol/l and mean serum potassium was ranging between 2.2±1 mmol/L. All patients were treated with oral potassium and alkali solutions along with steriods. *Conclusions:* The clinical implication of the present study is that RTA is a common feature of Sjögren's syndrome. It may be missed if the presentation is not due to oral and ocular symptoms.

Keywords: Sjögren's syndrome; Arterial Blood Gases analysis; Renal Tubular Acidosis.

Introduction

Primary Sjögren's syndrome (pSS) is a progressive autoimmune disorder involving the exocrine glands [1], typically presenting with keratoconjunctivitis and xerostomia [2]. It is characterized pathologically by a predominant lymphocytic infiltrate around epithelial ducts of exocrine glands on salivary gland biopsy [3] . Extra glandular manifestations of pSS, once thought to be uncommon, occur in up to 25% of patients. Patients can be afflicted by severe interstitial lung disease [4] ,cutaneous vasculitis[5], peripheral neuropathy[6] , and hematologic complications such as lymphoma [7]. They are also at increased risk for celiac sprue[8] and complications from Helicobacter pylori infection [9] such as mucosa-associated lymphatic tissue (MALT)-type lymphoma.

Much of our understanding of the clinical presentation of renal involvement in pSS is based on case reports [10–26] and small retrospective cohorts [27-29]. Tubulointerstitial nephritis (TIN) remains the most common presentation of renal involvement in pSS and CD4/CD8 T cell subsets are reported to predominate [27,30] . This is often characterized by a distal (type I) renal tubular acidosis (RTA) and less commonly proximal (type II) RTA (Fanconi syndrome) [11,31–33] . RTA , although, rare as initial manifestation, with only case reports available in the literature.

We examined the clinical findings , clinical trends and biochemical investigations of all patients with pSS who presented at our centre over 2 years and assembled a case series of patients with pSS with RTA .This case series aimed to describe the common clinical presentations of renal disease in pSS, the array of biochemical findings of renal involvement in pSS, and trends during follow-up and treatment.

Materials and Methods

Patient Selection

After institutional ethical board approval, a comprehensive search of the Out-patients and In-patients record was carried out in our centre, from January 2014 to May 2016 to identify patients with the diagnosis of pSS with RTA for this case series. Over this 2-yr time frame,113 patients of Sjögren's syndrome were identified.

Patients

All patients were from a nephrology outpatient and inpatient department of a tertiary care apex center in South India. Patients with a history suggestive of proximal muscle weakness of the lower or upper limbs, polyuria , were evaluated for etiology of RTA. Sjögren's syndrome was suspected in these patients when they presented with a history suggestive of dry mouth, dry eyes, gritty sensation of eyes, photosensitivity, red eyes, deposits of dried mucus in the corners of eyes, recurrent episodes of conjunctivitis, difficulty in swallowing food without fluid, joint pains, arthralagias and Raynaud's phenomenon. Several patients were referred to the nephrology department from the neurology and immunology department for evaluation of hypokalemic paralysis. Patients who presented with symptoms suggestive of RTA were then fully investigated to diagnose the cause of RTA.

General Laboratory Examinations

The patients underwent the routine laboratory tests, including peripheral blood cell count, erythrocyte sedimentation rate (ESR), serum C-reactive protein(CRP), hepatitis viral markers, protein electrophoresis, serum levels of total IgG, complement levels, rheumatoid factor(RF), cryoglobulins, screening for antinuclear antibodies (ANA), antibodies to native DNA, including anti-RouSSA and anti-LauSSB, detected by counter-immunoelectrophoresis with rabbit thymus extract and human spleen extract as substrates.

Renal Laboratory Investigations

Renal laboratory investigations included serum sodium, potassium, chloride, calcium, phosphorus, creatinine and in 24-h urine, venous pH and HCO3, urinalysis, 24-h urine protein excretion, urine culture, serum osmolality, urinary osmolality and urine pH.

Microscopic haematuria was defined by the presence of 2+ occult blood by dipstick analysis (Ames) and / or more than five red cells per high-power field. Pathological proteinuria was defined as 2+protein by dipstick analysis (Ames) and / or protein excretion of more than 250 mg / 24 h, measured by the turbidimetric assay with sulfosalicylic acid . Glomerular filtration rate (GFR) was estimated 4 variable MDRD formula.

Confirmation of Diagnosis

Patients were classified as having pSS using the 2002 American-European consensus classification criteria (35), which requires four of the following:

1. Ocular symptoms (dry eyes every day for more than 3 mo and / or use of tear substitutes more than 3 times a day);
2. Oral symptoms (daily feeling of dry mouth more than 3 mo, recurrent swelling of the salivary glands, or use of liquids to aid in swallowing of dry foods);
3. Ocular signs (positive Schirmer test or a Rose Bengal score of at least 4 of 9);
4. Histopathology with a focus score of 1 in a minor salivary gland biopsy;
5. Salivary gland involvement documented by a positive result in salivary scintigraphy, parotid sialography, or salivary flow testing;
6. Presence of auto antibodies to Sjögren's syndrome-associated antigen A [SSA (Ro)] and Sjögren's syndrome-associated antigen B [SSB (La)].

All 90 patients with Sjögren's syndrome underwent testing for antibodies to ribonucleoprotein antigens Ro (SS-A) and La (SS-B) at first visit.

Treatment

RTA was treated with an initial dose of sodium bicarbonate tablets (10-15 mmol / kg / day). The dose was modified after 4 weeks with the help of serum bicarbonate levels. Tablet prednisolone was given at a dose of 1 mg / kg / day for 12 weeks. It was tapered over the next 8 weeks. Potassium citrate syrup was

given to correct hypokalemia and 1,25-dihydroxyvitamin D supplementation was given to correct hypocalcaemia. Artificial tears with hydroxymethylcellulose were advised for dry eyes.

Follow-Up After the initial consultations the patients were advised followup once every 4 weeks for the first 6 months, later once every 3 months. Once the electrolyte abnormalities were corrected, except for maintenance doses of sodium bicarbonate, 1,25-dihydroxyvitamin D and potassium citrate, the other medications were either reduced to a minimum or stopped.

Table 1: Showing epidemiological data &clinical extraglandular manifestations in 11 patients

Sl No	Hosp no	age	sex	comorbids	Sr Cr	Hb G%	Act urine sediments	Proteinuria	Sr K	Positive schrimers test	Ph	Hco3	Dry mouth	Positive for SSA or SSB	Dry eyes
1	3729016	45	F	nil	0.6	7.3	nil	0.2	2.5	Yes	7.012	12	Y	Y	Y
2	2663164	47	F	lupus	1.1	9	yes	0.7	3	Yes	7.11	14	Y	Y	Y
3	3316437	36	F	lupus	1	12.4	yes	0.5	2.6	Yes	7.20	11	Y	Y	N
4	3720636	33	F	nil	0.7	9	nil	0.3	2.1	Yes	7.22	15	N	Y	N
5	1135000	41	F	nil	0.9	11	nil	0.1	1.9	Yes	7.08	13	N	Y	Y
6	3638528	39	F	nil	0.6	13	nil	0.3	1.8	Yes	7.014	11	N	Y	N
7	1202681	40	M	Htn	0.9	10.4	nil	0.1	1.6	Yes	7.21	12	Y	Y	N
8	3433975	41	F	nil	0.8	8.1	nil	0.2	2.2	No	7.12	14	Y	Y	Y
9	3709533	21	F	nil	0.9	9.8	nil	0.1	2.8	No	7.21	10	N	Y	Y
10	1304321	60	F	nil	1.2	12.2	Nil	0.4	2.3	no	7.054	11	Y	Y	N
11	2180028	40	F	Htn	1.1	12	Nil	nil	3.2	no	7.123	13	y	y	y

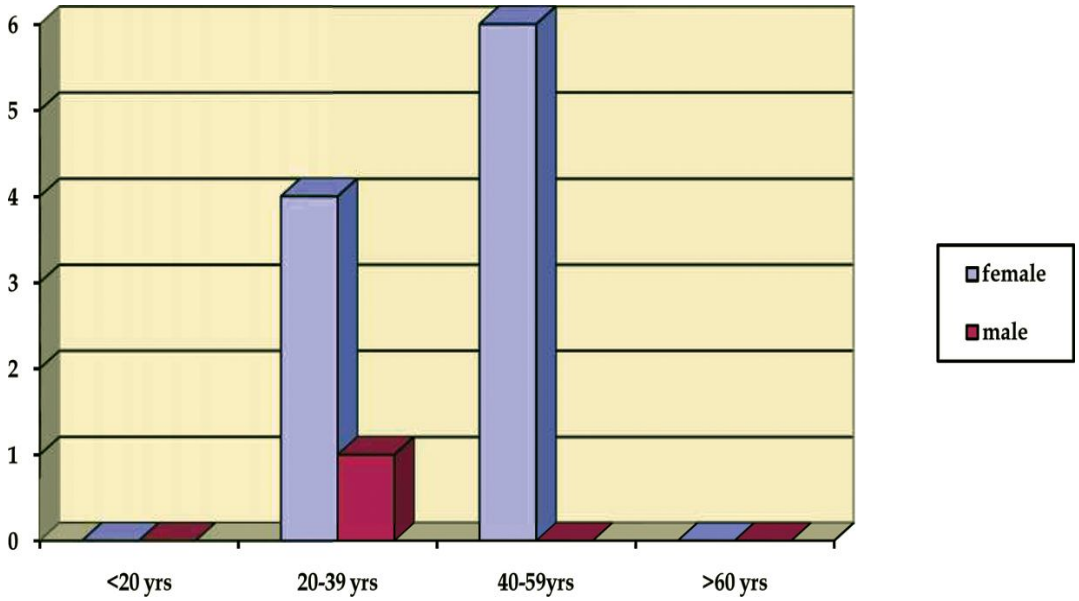

Fig. 1: Showing age & sex distribution of patients

Results

Demography

In this study, 113 Sjögren's syndrome patients were diagnosed between January 2014 to May 2016.The total number of RTA patients with Sjögren's syndrome diagnosed during this period was 11. The mean age at presentation was 40 (range 20–60) years and all most all were females except one male.

Clinical Features

113 patients ,who satisfied the 2002 American-European consensus classification criteria were included in the study. Of 113 patients, 11 patients (9.7%) who had features of RTA with hypokalemia were studied.

Oral and ocular symptoms were present in seven of patients. Dental caries were present in eight of patients. While the difficulty in standing and / or in gait, the flaccid paralysis, polyuria, body pains were

as in the Table 2.

The average age group was 30 to 40 years (Figure 1) Two patients had overlap serology positive for lupus (also had active urine sediments) and two had hypertension. All patients had normal renal functions. Five patients had anemia. Only three patients had proteinuria > 300mg/day. Serum potassium was ranging between 1.5 to 2.8 mmol/L (Figure 3). Average ABG pH was 7.12+/-0.12 with average serum bicarbonate 13 +/-2mmol/L (Figure 2). Seven Patients had serology positive for Ssa and four were positive for ssb. Seven patients having dry mouth and seven patients had dry eyes.

Table 2: Clinical features of Sjögren's syndrome patients with RTA (n=11).

Parameter	Patients ;n (%)
Females	10 (91%)
Symptoms at presentation	
Oral symptoms	7 (63.6%)
Ocular symptoms	7 (63.6%)
Difficulty in standing and/or in gait	4 (36.3%)
Flaccid paralysis	3 (27.2%)
Dental caries	5 (45.4%)
Body aches	8 (72.7)
Patients with SLE overlap	2 (18%)
Patients with hypothyroidism	5 (45%)

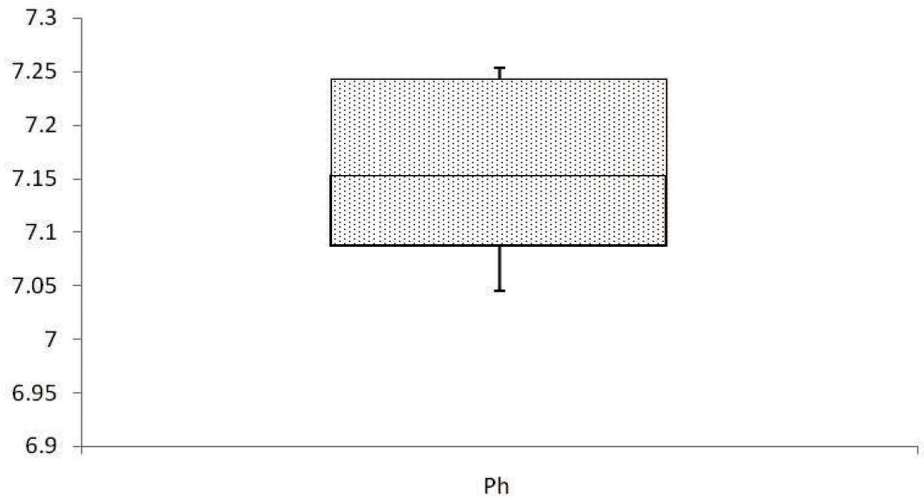

Fig. 2: Distribution of Ph in patients with Sjögren's Syndrome.

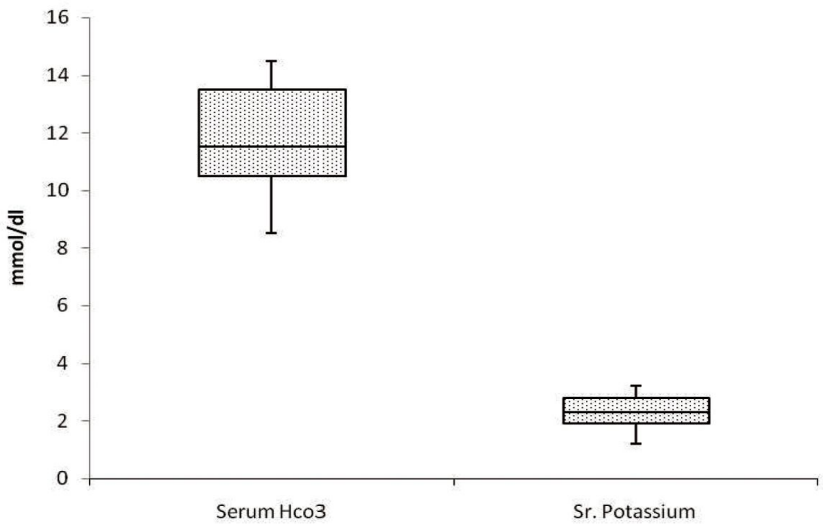

Fig. 3: Distribution of serum potassium and Serum Bicarbonate in patients with Sjögren's Syndrome

Table 3. Laboratory parameters of Sjögren's syndrome patients with RTA (n=11)

Investigation	Results
eGFR*, ml/min/1.73 m2	110± 13
Serum creatinine, mg/dl	0.9± 0.3
Blood urea, mg/dl	20 ± 8
Serum albumin, g/dl	3.1 ±0.8
Serum globulins, g/dl	4.8 ± 0.7
Hemoglobin, g/dl	9.5± 2.5
ANA positivity	2 (18%)
Anti-dsDNA positivity	2(18%)
Nephrotic range proteinuria	nil
Anti-Ro (SS-A) positivity	7 (63%)
Anti-La (SS-B) positivity	4 (36%)
Both anti-Ro (SS-A) and anti-La (SS-B) positivity	3 (27%)

Table 3: Laboratory parameters Sjögren's syndrome patients with RTA (mean ± SD)

Serum pH	7.12± 0.12
Serum uric acid,mg/dl	4 ±1
Serum bicarbonate, mmol/l	13.03 ± 2
Serum anion gap, mmol/l	9±1.5
Serum potassium, mEq/l	2.2±1
Serum sodium , mEq/l	140±5
Serum chloride, mEq/l	98±7
Serum calcium, mg/dl	7.5±2
Serum phosphorus, mg/l	3.5 ± 0.8

Discussion

Since there is as yet no single specific symptom or test to accurately diagnose Sjogren's syndrome, various criteria sets have been proposed by different authors [2,11]. Our study was designed to evaluate the incidence of RTA in a large group of patients with primary Sjögren's syndrome diagnosed according to the American-European consensus classification criteria.The homogeneous make-up of our study gave us the opportunity to outline certain aspects of renal involvement in primary Sjogren's syndrome, which have been controversial in the literature.

The prevalence and type of renal involvement in primary Sjogren's syndrome are unclear. In the literature, the frequency of renal abnormalities varies from 16% to 67% [5–8,20–24]. Several reasons may account for this discrepancy. The first is that only small groups of patients with Sjogren's syndrome were studied for renal involvement. The second is the lack of well-defined and commonly accepted criteria for diagnosing primary Sjogren's syndrome. Third, in some studies, primary and secondary forms of Sjogren's syndrome were analyzed together making it difficult to understand whether renal involvement should be ascribed to Sjogren's syndrome per se, or to associated disorders. Thus, the true prevalence of renal disease in primary Sjogren's syndrome remains uncertain, and studies involving larger patient groups with diagnoses according to highly valid and reliable criteria are still needed. In our sjorens patient population, the prevalence of RTA was 9.7%. This indicates tubular dysfunction is present in 10% of patients with sjorens syndrome. In another study by ram et@l, the prevalence of sjorens in RTA was 35 %.

Renal involvement in Sjogren's syndrome may be frequently latent. Clinically overt signs of renal disease were found in a minority of our patients. Three patients manifested as hypokalaemic paralysis. Signs of renal involvement, such as urine abnormalities and tubular defects, were most commonly identified in the absence of apparent clinical manifestations. This suggests that clinically evident renal disease is rare in patients with primary Sjogren's syndrome and that the presence of subclinical renal dysfunction, usually ascribed to tubulo-interstitial nephritis of variable degrees, may be detected by means of appropriate tests.

RTA may precede the onset of the subjective sicca syndrome, considered to be the classical manifestation of Sjogren's syndrome. In four of our patients, RTA antedated by several months the onset of ocular and oral symptoms. Renal disease preceding the onset of sicca syndrome has already been reported in patients with primary Sjogren's syndrome. Tu et.al [5] first described a patient whose chief manifestation of Sjogren's syndrome

was nephrogenic diabetes insipidus, which antedated by many years the onset of ocular and articular abnormalities. Subsequently, distal renal tubular acidosis and urolithiasis preceding subjective sicca symptoms have been reported in three different studies examining Sjogren's syndrome [5,28,29]. These findings make it clear that evidence for Sjogren's syndrome should be sought in adult patients with unexplained clinical and laboratory features of interstitial nephritis that lack the typical characteristics of chronic pyelonephritis, even in the absence of subjective sicca syndrome.

In a previous study, Shiozawaet al. [22] found that patients with Sjogren's syndrome showing tubular defects were significantly younger ,had a longer disease duration and had a lower creatinine clearance. Subsequently, Viergever and Swaak [24] found that ANA was more frequent in patients with abnormal tubular tests, suggesting that more severe autoimmunity may increase the risk of renal involvement. A bias in patient selection may explain these differences. However, the observation that our patients with renal involvement had a shorter disease duration is equally noteworthy, and may further support the concept that there is no set temporal order symptom appearance in this disease [1,5,7]. Thus, it should be expected that some patients show visceral involvement, such as a renal defect ,before the clinical occurrence of sicca symptoms, which usually determine the diagnosis of Sjogren's syndrome.

Limitations of the study were: retrospective in nature, minor salivary gland biopsy and Fractional Excretion of Bicarbonate to differentiate distal and proximal RTAs were not done due to financial constraints and patients discomfort.

In conclusion, the present study indicates that renal involvement is a frequent extra glandular manifestation of primary Sjogren's syndrome. The renal involvement is rarely overt, and more often follows a subclinical course. In some cases, it may precede the onset of subjective sicca syndrome.

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Original Article

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Clinical Study and Management of Bladder Outlet Obstruction in Adult Men

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Abstract

Introduction: Bladder outlet obstruction is one of the commonest causes of LUTS. Most common cause of BOO in men is BPH. Other common causes are bladder stones and bladder cancer. There is also increased incidence of BOO in younger age group too. In younger age group urethral stricture is commonly seen. *Aims and objectives:* To study various etiology and clinical presentations and management of bladder outlet obstruction according to standard surgical guidelines using either minimally invasive or conventional means. *Materials and Methods:* A total of 100 cases were admitted in Deccan College of Medical Sciences and Owaisi Hospital and Research Centre, Hyderabad, India from 1st September 2011 to 31th August 2013 with objective evidence of bladder outlet obstruction and study was conducted accordingly. *Discussion:* This study is a prospective observational study. The most common cause of BOO was evaluated and was treated according to standard line of treatment and follow up done accordingly. *Conclusion:* Bladder outlet obstruction is a clinical entity of diverse etiology and is a potentially curable illness if diagnosis is made early and treated according to the standard guideline of management. In patients not fit for surgery obstruction can be relieved by catheterization and treatment can be planned once patient is fit for definitive procedure. A further population based study is needed to identify the exact prevalence of BOO in different age groups and effectiveness of available modality and long term complications.

Keywords: Bladder outlet Obstruction; LUTS; BPH; Urethral Stricture.

Introduction

BOO is a common cause of LUTS in men. Most common cause of BOO in men is BPH. Other common causes are bladder stones and bladder cancer. Due to increased life expectancy there is an increased incidence of bladder outlet obstruction. For example, BPH is the most common cause of BOO In men above 70 years. There is also increased incidence of BOO in younger age group too. In younger age group urethral stricture is commonly seen.

Complications of BOO can be devastating. Long term or high grade BOO can permanently damage all parts of the urinary system. Complications include: bladder and kidney stones, kidney failure, recurrent UTI, urinary retention, urinary incontinence. Early diagnosis is important and can often lead to a simple and effective cure.

Numerous gender specific etiologies are responsible for BOO. BOO may be induced by specific functional and anatomical causes. The resulting obstruction frequently produces LUTS. Categorizing and understanding these entities is crucial as specific diagnostic modalities may be used to fully delineate the degree of BOO and any secondary

issues. Although urodynamic evaluation and pressure flow evaluation is the gold standard diagnostic tool, other modalities may also be used including post void residual analysis, urinary flow rate, cystoscopy and selected radiologic ones. Patients self appraisal of symptoms using IPSS is relevant to the initial assessment and subsequent longitudinal follow up.

Aims and Objectives

To study various etiology and clinical presentations and management of bladder outlet obstruction according to standard surgical guidelines using either minimally invasive or conventional means.

Inclusion Criteria

1. Any adult male comes with symptoms suggestive of BOO.
2. Above 18 years age group male patients.
3. Patients visiting first time for the symptoms to our institution.
4. Patient's consent for the thesis.

Exclusion Criteria

1. Patient's refusal for the thesis work.
2. Patients already on treatment for symptoms suggestive of BOO before coming to our institution.
3. Female patients.
4. Male patients below 18 years of age.
5. Patients already taken treatment for BOO in the past.

Materials and Methods

A total of 100 cases were admitted in Deccan College of Medical Sciences and Owaisi Hospital and Research Centre, Hyderabad, India from 1st September 2011 to 31th August 2013 with objective evidence of bladder outlet obstruction. The causes of obstruction as follow BPE (55%), carcinoma of prostate (9%), urethral stricture (15%) (Fig: 1), bladder cancer (8%) (Figure 3) and vesical calculus (13%) (Figure 2).

Ultrasound was the initial modality to diagnose BOO. X-ray KUB, I.V.P. series and CT [1-4] abdomen and pelvis were carried out were ever it was necessary, apart from the routine investigations. Serum PSA and prostatic biopsy was done in cases of suspected carcinoma prostate. Cystoscopy was performed in suspected cases of bladder cancer and biopsy was taken.

In cases of BPH, prostatic size more than 100cc was treated by open prostatectomy [5,6] and less than 100cc either medical management [7] (alpha blockers) or TURP [8], patients with less than 100g prostate, who were unfit for surgery and not willing for surgery, alpha blockers were given. For open prostatectomy [9,10], freyer's procedure was done as described in literature. After 14days suprapubic catheter was clamped and 3 way urethral catheter was removed. If patient had no voiding difficulties, suprapubic catheter was removed after 1day. Most of the patients had no major post operative complications.

Medical management using alpha blockers like tamsulosin 0.4mg HS and combination therapy given to patients. TURP [11] was done using STORZ IGLESIAS resectoscope with 30 degree telescope. 3 way urethral catheters removed after 5days. 5 patients out of 45 complained of poor urinary stream, which gradually improved within 1week and had no surgical intervention. Rest had no complications and followed up regularly.

Early stages of carcinoma prostate were treated with radical prostatectomy. All cases of carcinoma prostate were late stage. In cases of late stage carcinoma prostate (stage III & IV), maximum androgen blockade by orchidectomy using scrotal incision and postoperative anti androgen was given. Those prostate refractory to antiandrogen, chemoradiation [12] was advised. 8 patients responded well to B/L orchidectomy and anti androgen therapy. Only 1 patient had progressive elevation of serum PSA at 3months of follow up following maximum androgen blockade. He was advised chemoradiation.

For cases of bladder cancer with obstruction, radical cystectomy with ileal conduit was done. All 8 cases had uneventful post op.

Cases of bladder stone with size more than 3cms were treated by cystolithotomy and size less than 3cms were removed by cystolithotripsy. Cystolithotomy done using vertical midline incision, bladder closed in two layers using catgut 1-0 and 2-0. Suprapubic catheter removed after one week and urethral catheter two days after suprapubic catheter. In cystolithotripsy cystoscope is used to visualised

stone. Fragmented using lithotripter and removed. Urethral catheter is removed after 2 days.

Cases of stricture urethra managed with VIU. In cases of stricture following urethral rupture, immediate trocar suprapubic catheterization was done to relieve bladder outlet obstruction followed by radiological evaluation and managed by VIU. All cases of stricture were less than 3cms managed by VIU.

Subsequent to the definitive procedure patients were followed up for a periods ranging from 3 to 6 months followed by every yearly. Symptom improvement, physical examination and ultrasound were the main diagnostic tool for follow up. Serum PSA was done every 3months for follow up cases of carcinoma prostate, in addition to ultrasound. In rest of the cases of bladder outlet obstruction follow up done as described above.

Analysis and Results

During this study a total of 100 cases with objective evidence of bladder outlet obstruction were studied and the age distribution is as shown in diagram. The mean age is 57 years with range from 18 years to 90 years. The peak incidence is seen in 7th decade, followed by 8th and 5th decade. Least incidence was seen in 2nd decade (Table 1). The most common cause was BPH followed by stricture urethra, vesical calculus, carcinoma prostate and bladder carcinoma (Table 2). Out of 100 cases of BOO, 45 underwent TURP, 08 cases were treated with medical therapy, 2 cases underwent

Table 1: Age distribution

Age in years	No. of patients
Less than 20	01
20-29	03
30-39	03
40-49	16
50-59	09
60-69	42
70-79	19
80 and above	07

Table 2: Etiology

Etiology	No. of Patients
BPH	55
Carcinoma prostate	09
Bladder carcinoma	08
Bladder stones	13
Urethral stricture	15

Table 3: Management

Management	No. of patients
TURP	45
Medical management of BPH	08
Open prostatectomy	02
B/L Orchidectomy	09
VIU	15
Radical cystectomy and ileal conduit	08
Cystolithotomy	04
cystolithotripsy	9

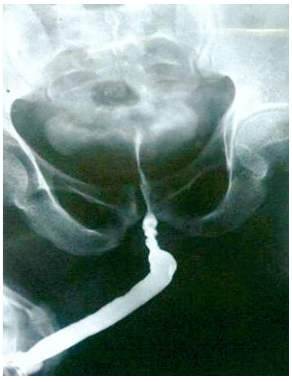

Fig. 1: RGU showing stricture urethra

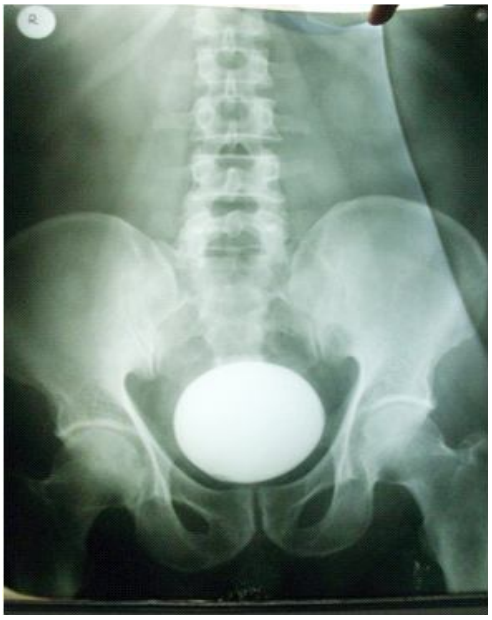

Fig. 2: Vesical calculus

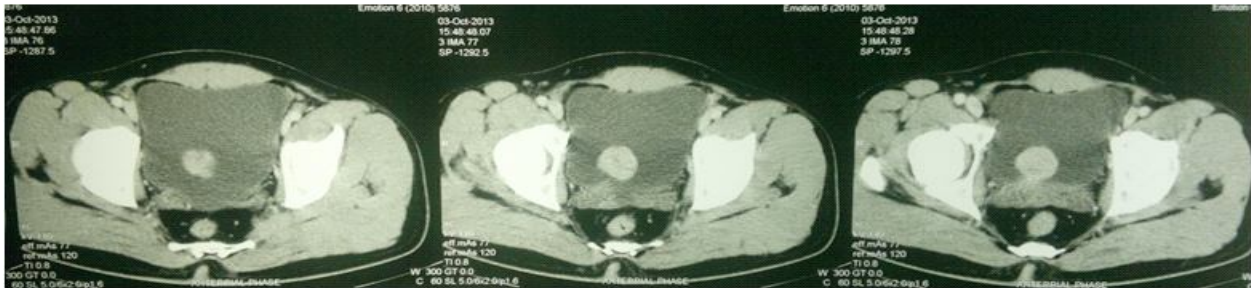

Fig. 3: CECT Abdomen & pelvis showing bladder tumor

open prostatectomy, 9 underwent cystolithotripsy, 9 underwent B / L orchidectomy, 8 underwent radical cystectomy with ileal conduit, 15 underwent VIU, 4 underwent cystolithotomy (Table 3).

Discussion

This study is a prospective observational study in which a total number of 100 cases of BOO were studied. The most common cause of BOO was BPH accounting for more than half the number of cases. Patient who underwent TURP had less morbidity, less complications and short duration of stay compared to open prostatectomy. Patients who were on medical treatment (unfit for surgery and those not willing for surgery) had less symptomatic improvement compared to TURP. Those who opted for surgery had better symptomatic improvement. Of the procedure mentioned above TURP seems to be better accepted by patients of BPH. In this study all cases of carcinoma prostate presented late underwent maximum androgen blockade. This implies significance of screening for early detection of carcinoma prostate. Cases of vesical calculus, those underwent cystolithotripsy had less morbidity and shorter hospital stays compared to those who underwent suprapubic cystolithotomy. Cystolithotripsy considered being better approach than cystolithotomy in treating vasical calculus. Cases of urethral stricture underwent VIU as had short segment of stricture and had good symptomatic improvement. Those who underwent radical cystectomy and ileal conduit for carcinoma bladder had advanced staging of disease but had better disease progression free survival. Few cases of primary bladder hypertrophy and bladder neck stenosis came to our institution for treatment but those were either had taken treatment some were else or they were already on treatment before coming to our institution hence not included in this study.

Conclusion

Bladder outlet obstruction is a clinical entity of

diverse etiology and is a potentially curable illness if diagnosis is made early and treated according to the standard guideline of management. The immediate obstruction can be relieved by catheterization either urethral or suprapubic. In patients not fit for surgery obstruction can be relieved by catheterization and treatment can be planned once patient is fit for definitive procedure. A further population based study is needed to identify the exact prevalence of BOO in different age groups and effectiveness of available modality and long term complications.

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Original Article

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Analysis of Hepcidin, Ferritin, CRP and Iron Levels in ESRD Patients and Their Correlation in CKD-4 & 5 Stages with/without Iron Intake

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Abstract

Inflammation interferes with iron utilization in chronic kidney disease through hepcidin. In our study, iron levels, ferritin, CRP and hepcidin levels were analyzed in newly diagnosed end-stage renal disease (ESRD) patients. A total of 50 ESRD patients and 5 healthy controls were studied. 40 recently detected ESRD patients on hemodialysis and 10 patients with Stage 4 CKD not received HD or parenteral iron, 22 out of 40 ESRD patients had already received prior parenteral iron or blood products. The ESRD patients had a significantly lower estimated albumin; and higher transferrin saturation (TSAT) and raised serum ferritin and Hepcidin levels. Hepcidin levels correlated significantly with Ferritin levels. Whereas ferritin levels correlated significantly with CRP levels. There have been elevated serum hepcidin levels in ESRD patients more in those receiving Iron therapy. High hepcidin levels could explain the functional iron deficiency. Larger randomized multicenter studies could throw more light on the diagnostic and therapeutic potentials of using Hepcidin-25 levels in regular practice.

Keywords: Chronic Kidney Disease; Hepcidin; CRP; Hemodialysis.

Introduction

The burden of chronic kidney disease (CKD) is increasing all over the world including in India. The best-known adverse consequence of CKD is end-stage kidney disease (ESRD). The incidence of ESRD in India has been estimated at 165–225 per million population [1].

The anemia that accompanies chronic renal disease (CKD) is associated with precocious mortality and morbidity rates, as well as with a decrease in life quality of patients. The chief etiology of anemia in CKD is erythropoietin (Epo) deficiency. Despite the widespread Epo use, over 50% of the patients do not reach the target hemoglobin levels[1,2]. The most common reason for poor response to Epo therapy is iron deficiency[1]. Inflammation has been implicated as another important cause of poor response[3]. C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) are acute phase reactants that have been used to reliably assess the degree of inflammatory activation [4]. Hepcidin, a regulator of body iron stores, has been identified to play a critical role in the pathogenesis of anemia of chronic disease.

Ferritin, other than being a marker of body iron stores, also increases in acute inflammation, and becomes less valuable as an indicator of iron status during inflammation [5]. However, studies have suggested that parenteral iron therapy might itself contribute to morbidity and mortality by inducing a pro-inflammatory state, due to increased oxidative

stress [6]. Additionally, assessment of iron status itself may be rendered difficult on account of inflammatory activation. A vast majority of Indians are vegetarians, and anemia due to iron deficiency is very common in the general population [7]. Hence, in our study, we analyze the body iron status, levels of CRP and hepcidin levels in ESRD population.

Materials and Methods

A non randomized cross sectional observational study was conducted at Narayana Medical College in the Department of Nephrology from January 2014 to January 2016. Study approved by Institutional ethics committee, a written informed consent was taken from all patients. All patients fulfilling inclusion criteria were screened and investigation done. Recently diagnosed ESRD patients on dialysis and CKD stage 4 of either sex were included. Healthy adult individuals were recruited as controls. The exclusion criteria were: The exclusion criteria were: age less than 18 years, evidence of acute infection or trauma in the last four weeks, history of parenteral iron injection in the last 14 days, history of blood transfusion in the last one month, hemoglobinopathies, malignancy, recent overt blood loss, and post-transplant status. 50 CKD patients including 10 patients with stage 4 CKD and 40 patients with ESRD who had been recently initiated on dialysis (< 3 months) and 5 healthy volunteers as controls.

All patients underwent a thorough physical examination, nutritional status and anthropometrical data, Skin fold thickness, mid arm muscle circumference (MAMC), Body fat percentage and Body mass index.

For dialysis patients, the modality and schedule of dialysis were also recorded. Hemogram, serum iron, total iron binding capacity (TIBC), serum ferritin, percentage transferrin saturation (TSAT), and quantitative CRP levels were analyzed. Anemia patients were stopped to oral iron for a week before sampling.

Serum Iron: Serum iron was measured as recommended by international committee for standardization. Protein was precipitated and chromogen was added to supernatant followed by measurement of absorbance

TIBC: Excess iron was added to sample as ferric chloride, excess unbound iron was removed with magnesium carbonate. The iron concentration was measured.

Serum Ferritin: Ferritin was estimated by an immunometric enzyme immunoassay.

Serum CRP: It was estimated using quantitative CPR assay kit, principle was based on immune precipitation in a liquid phase.

Serum Hepcidin: hepcidin-25 was estimated using the DRG® Hepcidin 25 bioactive ELISA (EIA-5258) hormone enzyme immune assay kit. The DRG Hepcidin-25 ELISA Kit is a solid phase enzyme-linked immunosorbent assay (ELISA), based on the principle of competitive binding.

The micro titer wells are coated with a monoclonal (mouse) antibody directed towards an antigenic site of the Hepcidin-25 molecule. Endogenous Hepcidin-25 of a sample competes with a Hepcidin-25-biotin conjugate for binding to the coated antibody. After incubation, the unbound conjugate is washed off and a streptavidin-peroxidase enzyme complex is added to each well. After incubation, unbound enzyme complex is washed off and substrate solution is added. The blue colour development is stopped after a short incubation time, turning the colour from blue to yellow. The intensity of colour developed is reverse proportional to the concentration of Hepcidin in the sample.

Statistical Analysis

Data were presented as mean ± S.E. ANOVA test was used to test the mean difference between three groups. Pearson correlation test was used to test the correlation between the variables. All the p value of less than 0.05 was considered as statistically significant.

Results

The study includes 55 individuals, 40 recently detected ESRD patients on hemodialysis and 10 patients with Stage 4 CKD not received HD or parenteral iron, 22 out of 40 ESRD patients had already received prior parenteral iron or blood products and 5 healthy control subjects. Males 39 and Females 16 were recorded. The mean age of patients in the study group was 48.76 ± 13.983 years. The minimum age of our individual are 20 years and maximum age was 74 years. The CKD-5 and CKD-4 patients had higher TSAT, CRP, Hepcidin and markedly raised serum ferritin levels (Table 1).

The hepcidin level, Ferritin level, CRP level, Transferrin Saturation levels were observed to be higher in CKD-5 group with Iron than CKD-5, CKD-4 without Iron . Hepcidin levels correlated

significantly with Ferritin levels [rho=0.589, p< 0.0001). Hepcidin levels correlated with Serum CRP [rho = 0.176] with no significant difference p>0.05). Ferritin levles correlated significantly with CRP levels [rho = 0.510, p< 0.0001) (Table 2) (Figure 1, Figure 2 & Figure 3).

Table 1: Characterization of various parameters in CKD patients and control subjects.

Disease	N	Hemoglobin	Transferrin Saturation	Ferritin	CRP	Mean Hepicidin	Mean MAMC	Mean Albumin	Mean TIBC	Mean Iron
CKD-4 without Iron	10	8.7900±1.65089	27.1080± 14.00924	215.00± 40.969	18.34± 16.334	27.6900± 13.04611				
CKD-5 without Iron	22	8.4318±1.92388	20.7186± 8.33124	275.36± 42.639	20.98± 16.059	66.6727± 40.91265	19.33 ± 2.99.61 (cm)	3.24± 0.50g/dl	263.91 ± 116.8	66.18 ± 27.4 g/dl
CKD-5 with Iron	18	8.2778±1.90466	35.6783±11.80983	401.94± 68.209	31.82± 30.878	116.3444± 65.86968				
Control	5	14.5400±1.16103	31.7400± 6.41779	43.20± 8.468	0.96±0.329	71.1691± 58.09552				

Table 2: Correlations between CRP, Hepcidin and Ferritin levels

Correlations				
		Serum CRP	Serum Ferritin	Serum Hepcidin
Serum CRP	Pearson Correlation	1	.510**	.176
	Sig. (2-tailed)		.000	.197
	N	55	55	55
Serum Ferritin	Pearson Correlation	.510**	1	.589**
	Sig. (2-tailed)	.000		.000
	N	55	55	55
Serum Hepcidin	Pearson Correlation	.176	.589**	1
	Sig. (2-tailed)	.197	.000	
	N	55	55	55

**. Correlation is significant at the 0.01 level (2-tailed).

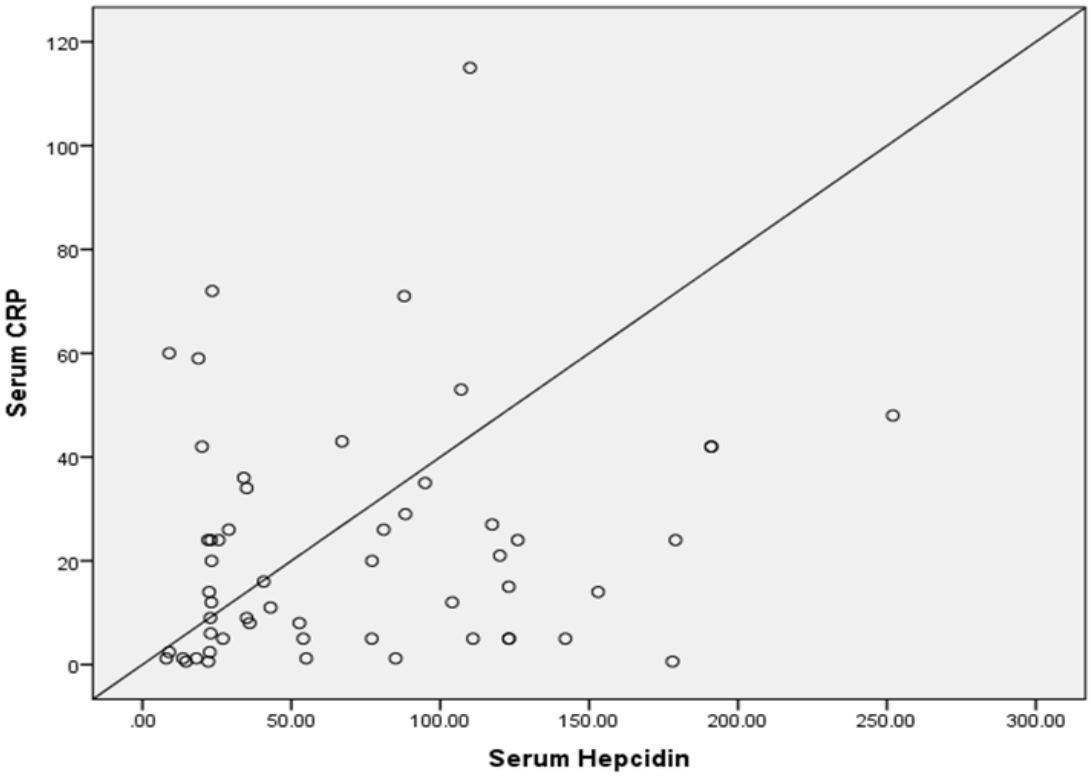

Fig. 1: Correlation between serum hepcidin & serum CRP [Scatter diagram]

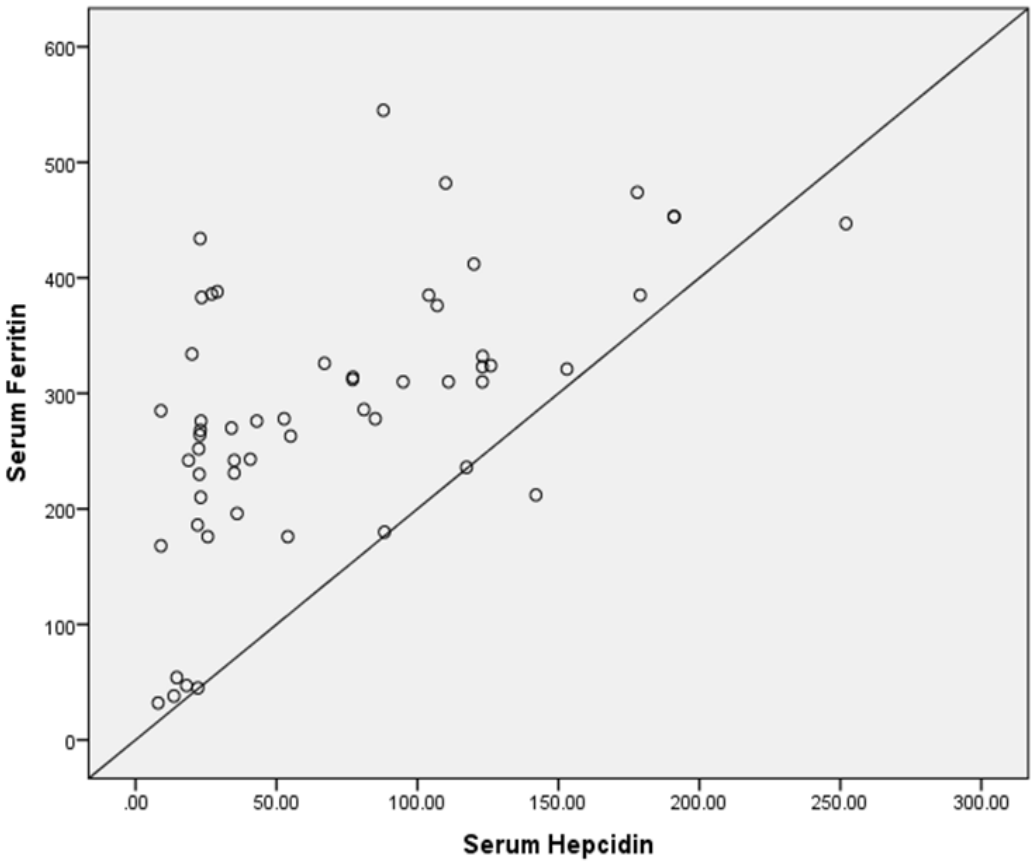

Fig. 2: Correlation between serum hepcidin and serum Ferritin [Scatter diagram]

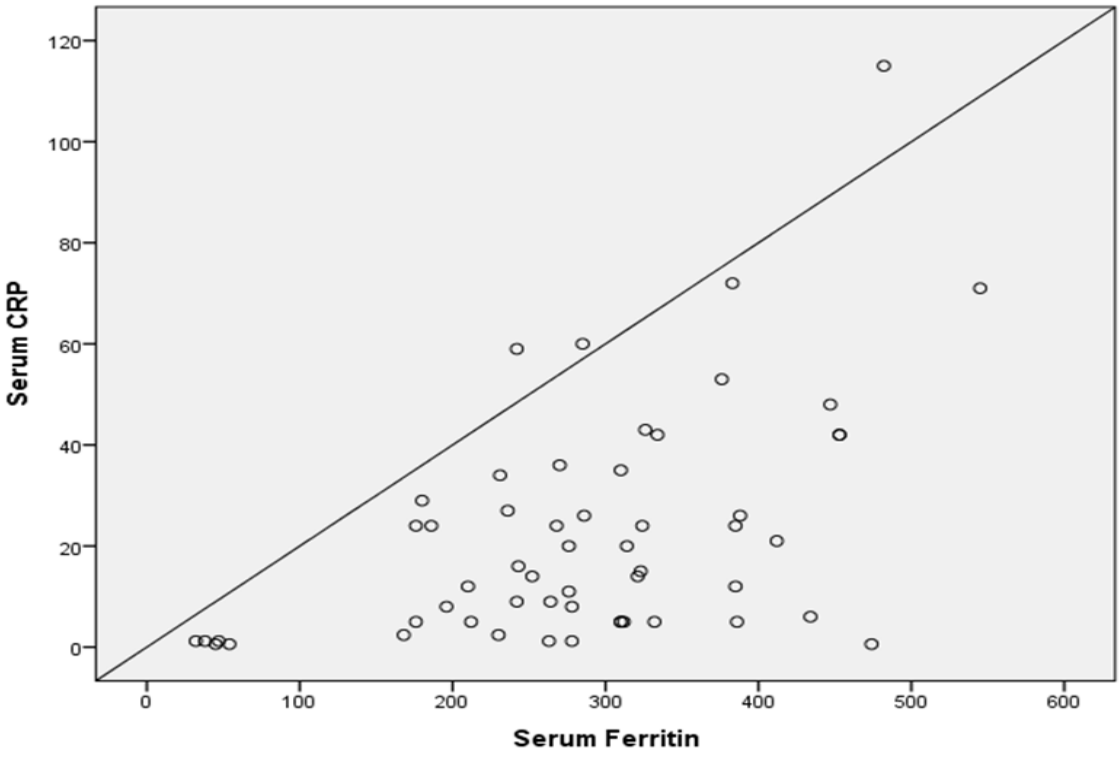

Fig. 3: Correlation between serum Ferritin & serum CRP [Scatter diagram]

Discussion

Iron deficiency is an important contributor to morbidity and mortality in ESRD. The cause is thought to be due to poor nutrition stemming from a predominantly vegetarian diet. Hepcidin, a regulator of body iron stores, has been postulated to play a critical role in the pathogenesis of anemia of chronic disease. Indian subjects have demonstrated to have micro inflammation and higher body fat percentage in healthy subjects as compared to Caucasians [8,9].

Hemoglobin levels in CKD-4/5 with/with out Iron intake shows less when compare with control subjects. Transferrin Saturation levels in CKD-5 with Iron intake shows high when compare with CKD-4 without Iron, CKD-5 without Iron and control subjects. Ferritin levels in CKD-5 with Iron intake shows very high when compare with CKD-4 without Iron, CKD-5 without Iron and control subjects. CRP levels in CKD-5 with Iron intake shows very high when compare with CKD-4 without Iron, CKD-5 without Iron and control subjects. Hepicidin levels in CKD-5 with Iron intake shows very high when compare with CKD-4 without Iron, CKD-5 without Iron and control subjects.

In our study there has been inflammatory activation with S.CRP levels increased in all study group. The cause of elevated mean CRP in subjects who did receive parenteral iron are on Hemodialysis is probably due to exposure to dialysis membranes, activation of immune cells (monocytes & T cells), or co-existing subclinical infection. A similar study done by V. Jha et al revealed inflammatory activation which was evident in 74 ESRD individuals has shown significantly higher CRP with (p value of < 0.001)[10]. Similar findings were noted in our study with significant correlation with hepcidin and serum CRP with significant p value (< 0.00).

In this study, the major finding was elevated hepcidin, in the study groups with subjects who did receive parenteral iron showed a higher S. hepcidin compared with subjects who didn't receive parenteral iron and control with significant (p value of < 0.01). A study done by Jha et al, revealed higher S. hepcidin levels in 74 ESRD patients with statistically significant (p value of < 0.12)[10]. Similar findings were noted in our study with increased serum hepcidin levels in ESRD individuals. Malyszko et al, revealed increased hepcidin level following I.V. iron therapy in Hemodialysis patients, but did not measure other inflammatory marker [11]. Comparing this study with our study group mean values of serum hepcidin was increased in CKD patients who were on haemodialysis and received i.v. iron therapy which was significant.

In our study S. ferritin was significantly elevated in subjects who did receive parenteral iron compared to individuals who didn't receive parenteral iron with statistically significant (p value of < 0.000). Ferritin was markedly increased due to iron overload in these subjects who did receive parenteral iron. V. Jha et al revealed elevated s. ferritin in individuals who did receive i.v. iron compared to individuals who didn't receive i.v. iron with p value (< 0.007)[10]. These findings were consistent with our study group individuals which showed significant statistically correlation between hepcidin and serum ferritin.

In our study there was no significant correlation between hemoglobin levels and s hepcidin levels. (p=0.138). Our study population consisted of only stage 4 and 5 CKD, the mean Hb levels were similarly low in all the groups of patients and had no relation to increasing s hepcidin levels. In our study, there was no significant correlation between hepcidin levels and TIBC (p=0.523). Serum Hepcidin & MAMC levels doesn't showed significant correlation (p=.240) could be established between these variables. Hepcidin & albumin levels did not show any correlation (p=0.511).

However in our study though CRP was significantly raised in the hemodialysis group, it is not correspondingly correlate with the elevated s hepcidin levels we had noted in this group.

Determination of hepcidin levels in CKD patients may not provide more diagnostic value than ferritin, but further studies are needed. Hepcidin and its regulatory pathways are potential therapeutic targets, which could lead to effective treatment of anemia of chronic disease and ESA hyporesponsiveness in CKD.

Atherosclerosis could induce an increase of the arterial IMT and arterial stiffening, and eventually lead to luminal obstruction with consequent ischemic events, such as myocardial infarction and stroke. Thus higher s hepcidin levels may be able to predict the subgroups of population with CKD who may be at higher risk for cardiovascular disease. This is an exciting area that needs to be further studied and may point the direction in which future strategies employing hepcidin as a diagnostic modality or as a target of directed therapeutic approaches.

Conclusion

There have been elevated serum hepcidin levels in ESRD patients more in those receiving Iron therapy.

High hepcidin levels would reveal functional iron deficiency. There was significant correlation between levels of hepcidin and iron status with inflammatory markers. The cause of the relatively greater degree of inflammatory activation as well as the relationship with parenteral IV iron administration needs further studies. Larger randomized multicenter studies could throw more light on the diagnostic and therapeutic potentials of using Hepcidin-25 levels in regular practice.

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Original Article

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Surgical Therapy in Infertile Men with Obstructive Azoospermia Due to Ejaculatory Duct Obstruction–Outcome after Transurethral Resection of Ejaculatory Duct

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Abstract

Objectives: To report our experience with transurethral resection of ejaculatory ducts (TURED) in infertile men with symptomatic ejaculatory duct obstruction. *Material and Method:* We studied 4 cases of ejaculatory duct obstruction from January 2014 to January 2015. Investigations included a history, physical examination, semen analysis, semen culture, hormone levels and trans-rectal ultrasonography. Results were evaluated after TURED, especially the semen parameters, the patency and the pregnancy rate. *Results:* Causes of obstruction were previous infection with inflammation, calculus and prostatic cyst. Mean age was 34 years.Mean Duration of infertility was 3.5 years.Mean FSH value was 1.5. Mean Semen volume was 0.5 ml with SD of ± 0.10m. In all patients fructose was absent on semen analysis. On TRUS mean seminal vesicle diameter was 16.00 mm Seminal vesicle was dilated in all cases. In 3/4 patients who had patency in follow up had a mean sperm count of 14.33 million/ml.Mean time to patency was 3 months.Post TURED ejaculate volume improved in all patients with mean of 1.75ml and SD of 0.50 ml. Patients who had undergone TURED reported a patency rate of 75 %, with one patient showing absence of sperms in follow up. After TURED on follow up pregnancy was reported in one case i.e. 25 %. In our study mean follow up was 10 months. *Conclusions:* Men with symptomatic EDO who underwentTURED showed improvements in theirejaculation, sensation of orgasm, semenanalysis values and fertility.

Keywords: Ejaculatory Duct Obstruction; Infertility; Ejaculatory Duct/Prostatic Cyst; Transurethralresection of Ejaculatory Duct; Tured.

Introduction: Infertility by itself does not threaten the life, but it has devastating psycho-social consequences on infertile couples. It remains a worldwide problem and challenge. Management of infertility has been and still a difficult medical task not only because of the difficulty in the diagnosis and treatment of the reproductive disorders in each partner, or the poorly unstated interaction between the partners' fertility potentials, but also because of the fact that success of treatment is clearly identifiable entity - the achievement of pregnancy. By following the *evidence-based* management protocol infertile couples will have a good chance to start up their treatment in the proper way at early time [1] .

Azoospermia, defined as complete absence of sperm from the ejaculate, is present in less than 2% of all men and in 15% of infertile men [2].

Among infertile men, the incidence of azoospermia is about 10 to 15%, of which 40% is due to obstructive azoospermia [3].

Causes of obstructive azoospermia are vasectomy, congenital absence of vas deferens and ejaculatory duct obstruction, and acquired diseases (eg,epididymal obstruction secondary to infection, vasal injury due to previous inguino-scrotal surgery) [4].

There are few diagnoses in azoospermic men that

are amenable to surgical correction. The most common among these are epididymal obstruction, vasectomy and obstruction of the ejaculatory ducts. The importance of diagnosing these conditions and treating them appropriately lies in the fact that they can be cured [4].

Ejaculatory duct obstruction (EDO)is reported to be the cause of azoospermia in up to 5% of patients [5].

In the present study we assessed and providedthe evidence for the effectiveness of surgical treatment of ejaculatory duct obstruction.

Objectives

To report our experience with transurethral resection of ejaculatory ducts (TURED) in infertile men with symptomatic ejaculatory duct obstruction and to assess the patency rate after trans-urethral resection of ejaculatory ducts.

Material and Methods

This study was carried out in Bharti Hospital and Research Center, Pune during the periodJanuary 2014 to January 2015. This study was done on 4 patients of Obstructive Azoospermia who were subjected to Transurethral resection of Ejaculatory ducts (TURED).

Ethics

The study protocol was reviewed and approved by institutional ethical and scientific committee and informed consent was obtained.

Statistics

Data analysis was carried out under the guidance of our statistics expert, using Statistical Package for Social Sciences version 17.

The Inclusion Criteria for TURED

1. The preoperative symptoms likeinfertility, non-projectile ejaculation, a decrease in sensation of orgasm, and/or pain with ejaculation, history of prostatitis or epididymitis, perineal or testicular pain.
2. Low volume ejaculate
3. Bilateral palpable vas deferens
4. Normal hormonal profile
5. Dilatedseminal vesicles on trans-rectal ultrasonography (TRUS)

The preoperative symptoms included infertility, non-projectile ejaculation, a decrease in sensation of orgasm, and/or pain with ejaculation etc. Investigations included a focused history and physical examination, two semen analyses, a semen culture (with PCR analysis), and TRUS. On TRUS, each man was evaluated for prostatic calcifications, ejaculatory duct cysts and the diameter of the seminal vesicles. Seminal vesicles were considered dilated when they were more than 15mm in diameter.

Surgical Technique

All operations were done under regional anaesthesia. Cystoscopy was performed and the bladder was inspected. Cysto-urethroscopy findings such as midline cysts and altered verumontanum anatomy etc. were recorded. A drape is used with a finger in the rectum to allow better depth perception and visualization of the posterior prostate. Using a transurethral resection set, cystic lesions were opened. If an ejaculatory duct cyst is present, it is usually deep and just posterior to the verumontanum. Therefore, the verumontanum is deeply resected with care not to injure the rectum. Once efflux from the ejaculatory ducts of copious cloudy material is present, the resection was considered adequate. Electrocautery is used judiciously to avoid occlusion of the newly opened ejaculatory ducts. Care is taken at all times to protect the bladder neck and external sphincter from injury that might result in retrograde ejaculation and urinary incontinence. A Foley catheter is left overnight and the patient was discharged next day. All the patients received a 5- to 7-day course of antibiotics. Vasogram or seminal vesiculogram were not done.

Postoperative Evaluation

All patients were assessed at 6 weeks and 3 months and included focused history about improvements in symptoms of EDO andsemen analyses and continued until pregnancy was achieved. Patency was defined as the presence of motile sperm in the ejaculate of at least one postoperative semen sample. Pregnancy was defined as unassisted establishment (no assisted reproduction) of a viable pregnancy leading to a live birth. Follow-up information was obtained from clinic visits and telephone contact.

Results

Etiology

In 50 % of patients with ejaculatory duct obstruction had history of previous infection with inflammation as a cause of obstruction.Other 25% had calculus and prostatic cyst as obstructive etiology [Figure 1].

Descriptive Statistics (Pre-operative parameters) [Table 1]

In 4 Patients who has Undergone TURED

i. Mean age was 34 with standard deviation of ± 2.65 with minimum age of patient seen was 32 and maximum age was 38 years.

ii. Mean Duration of infertility was 3.5 years with standard deviation of ± 2.38. Minimum duration of infertility was 1 year and maximum was 6 years.

iii. Mean FSH value was 1.5 with SD of ± 0.58

iv. Mean Semen volume was 0.5 ml with SD of ± 0.10ml. Minimum semen volume was 0.4 ml and maximum was 0.6 ml.

Fructose in Semen Analysis

In all patients who underwent TURED due to ejaculatory duct obstruction fructose was absent on semen analysis.

Patency in TURED Patients

Patients who had undergone TURED reported a patency rate of 75 %, with one patient showing absence of sperms in follow up.

Pregnancy Rate Post TURED

After TURED on follow up pregnancy was reported in one case i.e. 25 %.

Descriptive Statistics (Post-Operative Parameters) [Table 2]

In 4 Patients who has Undergone TURED

i. Mean operative time was 77 minutes with SD of ± 9.57. Minimum operative time required was 70 minutes and maximum operative time was 90 minutes.

ii. In 3 / 4 patients who had patency in follow up had a mean sperm count of 14.33 million / ml with SD of ± 6.81.Minimum sperm density seen was 9 million / ml and maximum was 22 million / ml.

iii. Mean time to patency was 3 months with SD of ± 1.0 .Minimum time required for patency was 2 months and maximum time was 4 months.

iv. In our study mean follow up was 10 months with SD of ± 1.63 .Minimum follow up was 8 months and maximum was 12 months.

v. On TRUS mean seminal vesicle diameter was 16.00 mm with SD of 0.82 mm.One patient had diameter of 17 mm while others have diameter more than 15 mm. Seminal vesicle was dilated in all cases.

vi. Post TURED ejaculate volume improved in all patients with mean of 1.75ml and SD of 0.50 ml.

Complications with TURED are rare if the procedure is done carefully and with expertise. In our study, overall there were no complications associated with the procedure.

Table 1: Descriptive Statistics (Pre-operative parameters)

	N	Minimum	Maximum	Mean	Std. Deviation
Age	4	32	38	34.50	2.65
Duration of Primary infertility(years)	4	1yr	6 yrs	3.50	2.38
FSH	4	1.0	2.0	1.50	0.58
Semen volume	4	0.4ml	0.6ml	0.53	0.10

Table 2: Descriptive Statistics (post-operative parameters)

	N	Minimum	Maximum	Mean	Std. Deviation
Operative time	4	70	90	77.50	9.57
Sperm density (million / ml)	3	9	22	14.33	6.81
Time to patency (month)	3	2	4	3	1
Follow up(month)	4	8	12	10.00	1.63
On TRUS Seminal Vesicle in Millimeters (mm)	4	15	17	16.00	0.82
Post TURED ejaculate vol.	4	1	2	1.75	0.50

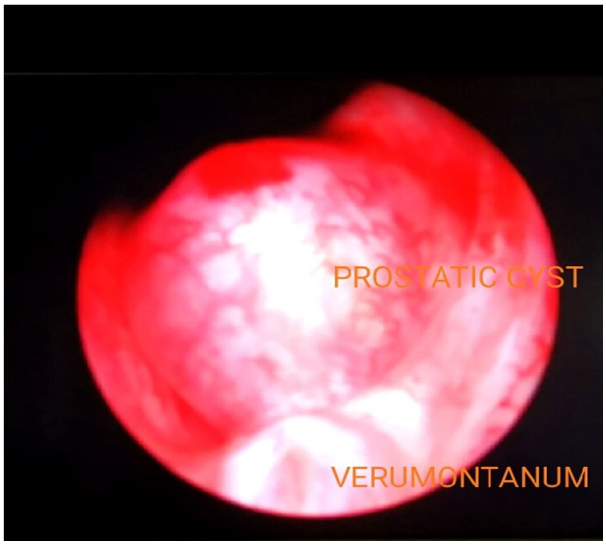

Fig. 1:

Discussion

For patients with obstructive azoospermia, surgical therapy is an acceptable management option in comparison with assisted reproduction techniques (ART) such as ICSI, which tend to bypass the male factor etiology. Surgical correction offers a long-term solution and aims at correcting the underlying pathology. It also obviates the need for repeated ART each time the individual wishes to contribute to a pregnancy.

Ejaculatory duct obstruction is a rare cause of infertility, but it is essential to diagnose it, as it can be easily corrected with a minor cystoscopic procedure. Detecting Ejaculatory duct obstruction has become easier and less invasive with the development of high resolution TRUS, which by itself has been shown to be very effective for identifying possible EDO. It can show cysts or calcifications that might cause blockage, and identifies dilated seminal vesicles.

In patients with suspected EDO, TURED has become the standard procedure. It was described by Farley and Barnes in 1973 [6].

Etiology

Etiology of EDO is varied. Ejaculatory duct obstruction can be either congenital or acquired. Congenital causes include congenital atresia or stenosis of the ejaculatory ducts and utricular, mullerian, and wolffian duct cysts. Acquired causes may be secondary to trauma, either iatrogenic or otherwise, or infectious or inflammatory aetiologies. Calculus formation secondary to infection may also cause obstruction [7]. In our study 50 % of patients with ejaculatory duct obstruction had history of previous infection with inflammation as a cause of obstruction.Other 25% had calculus and prostatic cyst each as obstructive etiology.Paick J et al [8] in his study of 50 men the main cause of EDO was a midline cyst in 16, Wolffian malformation in four, tuberculosis in 17, previous genitourinary infection in five and idiopathic in eight men. In 17 patients the seminal vesicles appeared to be atrophied on TRUS; 15 of these patients had a history of pulmonary tuberculosis and subsequent vasography in five showed multiple bilateral vasal obstruction. Tu XA et al [9] in their study had 6 prostatic cyst and 3 cases of calcification out of total 60 cases.

Age

Patients of EDO are usually young individuals. In our study mean age was 34 with standard deviation of ± 2.65 with minimum age of patient seen was32 and maximum age was 38 years.Ozgok Y et al [10] in his study of 24 patients had mean age of 29 years with variation between 20 and 40 years (mean=29).Kochakarn W et al [11]in his study of 7 patients has age range from 32-45 years old (mean 34.5).

Duration of Infertility

In our study duration of infertility was 3.5 years with standard deviation of ± 2.38.Minimum duration of infertility was 1 year and maximum was 6 years.

Serum FSH Levels

Mean FSH value was 1.5 with SD of ± 0.58 in our study. Kochakarn W et al [11] in his study of 7 patients had seventy-one per cent patients with normal hormonal profiles and twenty-nine per cent had a slight increase of FSH, LH but not more than one fold of normal range.

Semen Values

Mean Semen volume was 0.5 ml with SD of ± 0.10ml in our study. Minimum semen volume was 0.4 ml and maximum was 0.6 ml. in the study by Christopher W et al R [12], the mean ejaculate volume before TURED was 1.1 mL. In study by Immo-Schroeder-Printzen et al [13], sperm analysis pre-operatively demonstrated typical low-volume ejaculates with azoospermia, ejaculate volume was between 0.5 and 1.6 ml (mean 0.95 ml) and seminal

pH was acidic in every case.

Fructose in Semen Analysis

In all patients who had undergone TURED due to ejaculatory duct obstruction fructose was absent on semen analysis.Immo-Schroeder-Printzen et al [13] in their of 16 patients with EDO,fructose was absent or below 13 μmol/ejaculate. Testicular volumes, serum FSH and spermatogenesis (Johnson score >8) were normal in all cases.

TRUS Findings

TRUS is certainly the easiest way to detect cystic lesions at the verumontanum level as well as dilatations of the internal ductal diameter and of the seminal vesicles. On TRUS mean seminal vesicle diameter was 16.00 mm with SD of ±0.82 mm in our study.Christopher W et al [12] On TRUS, each man was evaluated for prostatic calcifications, ejaculatory duct cysts and the diameter of the seminal vesicles. Seminal vesicles were considered dilated when they were = 12 mm in diameter. In study by Immo-Schroeder-Printzen et al [13] TRUS findings cover midline utricular and Müllerian cysts , as well as dilatated ejaculatory ducts, defined with an internal ductal diameter >2.3 mm and / or dilatated seminal vesicles with a cross-sectional diameter >15 mm.

Operative Time

Mean operative time was 77 minutes with SD of ± 9.57. Minimum operative time required was 70 minutes and maximum operative time was 90 minutes.

Post Turedejaculate Volume

Post TURED ejaculate volume improved in all patients with mean of 1.75ml and SD of ± 0.50 ml. Christopher W et al [12]The mean ejaculate volume after TURED increased to 2.3 mL.

Sperm Count

In 3 / 4 patients who had patency in follow up had a mean sperm count of 14.33 million / ml with SD of ± 6.81.Minimum sperm density seen was 9 million / ml and maximum was 22 million / ml. In study by Christopher W et al [12], the total motile sperm count increased 38.1 million per ejaculate. Ozgok Y et al [10] in his study of 24 patients before transurethral resection mean sperm count was 1.66x10(6) / ml compared to 25.4x10(6)/ml postoperatively. Kochakarn W et al [11] in his study of 7 patients 6 of 7 (86%) showed improvement of semen analysis. Up to one year, 6 of 7 (86%) have normal semen analysis and another one still had azoospermia.

Time to Patency

Mean time to patency was 3 months with SD of ± 1.0. Minimum time required for patency was 2 months and maximum time was 4 months.

Patency in Tured Patients

Patients who had undergone TURED reported a patency rate of 75%, with one patient showing absence of sperms. Yurdakul t et al [14] in his study before TURED, all patients were azoospermic, following the operation, sperms were seen in the ejaculates of 11 / 12 patients. Immo-Schroeder-Printzen et al in their of 16 patients with EDO had post-operative ejaculates showing patency in all patients with Mullerian cysts. There was an improvement in sperm counts in all Mullerian cyst patients with successful opening but only an improvement in two patients without cystic lesions. The worst results were obtained in all patients with lateral cystic lesions of the ductus ejaculatorius.

Pregnancy Rate Post Tured

After TURED on follow up pregnancy rate was reported to be 25% with follow up period of 8 – 12 months. In study by Christopher W et al [12] four of the six men available for long-term follow-up reported successful paternity without assisted reproduction techniques. In study by Yurdakul t et al [14] after a mean follow-up period of 12 (range 4-36) months, five (41.6%) pregnancies were noted.Ozgok Y et al [10] in his study of 24 patients had a mean follow-up period of 9 (6-18) months, 6 (25%) pregnancies were noted. Kochakarn W et al [11] in his study of 7 patients had a long-term follow-up, 4 of 7 (57%) were able to impregnate their wives. TuXa et al [15] in his evaluation of43 men with EDO treated by TURED, 36 (83.7%) showed improved semen parameters and 11 (25.6%) achieved pregnancies. Weintraubet al [16] reported 25% pregnancy rate in their study of eight patients with ejaculatory duct obstruction.

Follow up

In our study mean follow up was 10 months with SD of ± 1.63. Minimum follow up was 8 months and maximum was 12 months.

Conclusion

Abnormalities of the distal ejaculatory ducts especially related to infertility have been well documented with the advent and increased use of high-resolution TRUS. In an infertile male with oligospermia or azoospermia with low ejaculate volume, normal secondary sex characteristics, testes, and hormonal profile, and dilated seminal vesicles, midline cyst, or calcification on TRUS, ejaculatory duct obstruction is suggested.EDO is a very treatable disease that can be cured with a simple cystoscopic procedure. This treatment has a positive impact not only on fertility, but also on sexual satisfaction. Men with symptomatic EDO who underwent TURED showed improvements in their ejaculation, sensation of orgasm, semen analysis values and fertility.

Genetic testing and counseling should be considered in appropriate cases, because genetic factors may impact both the patient and his potential offspring, also not all patients post successful TURED are able to impregnate their spouse.

Current technology often allows for paternity for men previously labeled sterile. In general, if possible, it is preferable to improve the male's fertility potential and allow the couple to conceive by intercourse. This is not only economic but also provides the males great mental satisfaction.

Limitations

This is a non-randomised clinical study to evaluate TURED results. The availability of necessary instruments and expertise made the study feasible. However, long term prospective trials are necessary to validate the durability of this therapy and its effect on the symptoms of EDO.

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Original Article

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Histological Pattern of IgA Nephropathy (IgAN) by Oxford Classification by MEST Scoring

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Abstract

IgAN is one of the commonest biopsy proven primary glomerular diseases with diverse histological patterns based on the geographic location. This is a study was done by including all consecutive cases of biopsy proven IgAN(native kidney) performed at EMS Memorial Cooperative Hospital, Perinthalmanna, Kerala, India, from September 2009 to February 2016. We had 62 (Females: 36, Males: 26) cases of biopsy proven IgAN. The mean age of the patients was 37.71 years and male: female ratio was 1.38:1. The IgAN was classified according to the Oxford classification (MEST scoring). Majority of the patients had mesangial hypercellularity (91.94%) and tubular atrophy (69.36%; T1-43.55%, T2-25.81%). Only few patients had endocapillary proliferation (20.97 %), and segmental sclerosis (39.68 %). Glomerular crescents (involving 5-20% of glomeruli) were found in 4.84 % of patients with IgAN. The commonest combinations of MEST scoring were M1, E0, S0, T1 (25.81%), followed by M, E0, S1, T1 (14.52%) and M0, E0, S0, T0, was seen only in 6.45% of cases. This study confirms the aggressive nature of IgAN in Indian subcontinent, unlike western literature.

Keywords: IgAN; Oxford-MEST Classification.

Introduction

Immunoglobulin A nephropathy (IgAN) is one the most common glomerulonephritis worldwide [1-6]. The bulk of the disease burden is borne by Asian countries [2-6]. The Oxford classification (MEST) of IgAN was proposed in 2009; found that mesangialcellularity, endocapillary proliferation, segmental sclerosis and tubular atrophy / interstitial fibrosis, to have independent predictive value on clinical outcome [7] Recent trials from Europe and North America have validated its utility [8-10]. However, its clinicopathologic spectrum in Asian and South American countries is not well documented except for few studies [11-14].

Aims and Objectives

To classify the patients of biopsy proven IgAN based on MEST Oxford- classification.

To analyze the histological combinations of MEST scoring in IgAN.

Meterials and Methods

This is a retrospective study which included all consecutive patients with diagnosis of IgAN on light and immunofluorescence microscopy. The biopsies performed at EMS Memorial Cooperative Hospital and Research Centre, Perinthalmanna, Kerala, from September 2009 to April 2016, under guidance of ultrasound using Bard® Max-Core® disposable core biopsy instrument, CR Bard Inc., USA. All the biopsies were analyzed by light microscopy using hematoxylin and eosin (H&E), periodic acid Schiff (PAS), Jone's silver methaneamine and Gomori's trichrome stains (MT) and immunofluorescence studies were performed using anti-human IgG, IgA, IgM, C3, C1q, kappa and lambda light chains. The IgAN was diagnosed in presence of IgA-dominant mesangial or immune deposits (> 2+ and the absence of C1q deposition) through immune fluorescence (IF) microscopy. The data was analyzed by SPSS 17 for Windows, by SPSS Inc. IL, USA. Two-sided p value of < 0.05 was considered as statistically significant.

The IgAN was classified according to the Oxford-MEST classification [mesangial hypercellularity score (M; M0 < 0.5, M1 >0.5), the presence of endocapillary proliferation (E; E0: absent, E1: present) and segmental glomerulosclerosis / adhesion (S; S0: absent, S1: present), and the severity of tubular atrophy / interstitial fibrosis (T; T0 <25%, T1: 26–50%, T2 >50%) [7].

Results

A total of 271 patients underwent renal biopsy during the study period. The IgAN was diagnosed in 62 out of 271 (22.88%) patients, and was most common biopsy proven renal disease in the study. Among those with IgAN, 36 were males and 26 were females; with M: F ratio of 1.38:1. The age of subjects ranged from 12-75 years (Mean:37.71, SD: 14.21) and majority (62.90%) were of < 40 years of age. Both males and females were of similar age (Table 1); the difference was statistically insignificant (p:0.20).

The indications of renal biopsies in the study were; microhematuria in 3, subnephrotic protienuria in 3, subnephrotic proteinuria with haematuria in 13, nephrotic syndrome in 4 and renal insufficiency (serum creatinine >1.4mg / dl) with proteinuria and haematuria in 39 subjects. Among those with renal insufficiency 28.21 % (11 out of 39) had severe failure (eGFR < 30 ml / min / 1.73m2), 69.23 % (27 out of 39) had moderate renal insufficiency (eGFR 30 to 59 ml / min / 1.73m2) and 2.56 % (1 out of 39) had mid renal insufficiency.

The patients were categorised based on indication for renal biopsies and results of MEST scoring are represented in figures 1 to 6. Frequencies of MEST score combinations in the study are listed in Table 2. Overall prevalence of M1, E1, S1, T1 and T2 was noted in 91.94, 20.97, 39.68, 43.55 and 25.81% of renal biopsies respectively. The commonest combinations of MEST scoring were M1, E0, S0, T1 (25.81%), followed by M, E0, S1, T1 (14.52%) and M0, E0, S0, T0, was seen only in 6.45% of cases. 3 out of 62 (4.84 %) patients also had associated extracapillary proliferation in the form of fibrocellular crescents in renal biopsy. There was statistically significant correlation of indication of biopsy with presence of M1 (p:0.008) and TA (tubular atrophy T1 or T2) (p:0.018) on univariate analysis, however, it was insignificant with E1 (p:0.374) or S1 (p:0.295).

Multivariate analysis of indication of biopsy with MEST scoring showed a statistically significant correlation with presence of TA (p:0.003); whereas, it was not significant with M1 (0.689), E1 (0.272) or S1 (0.30). There was no statistically significant effect of gender or age on MEST score on multivariate analysis.

Mesangial Hypercellularity

The majority of the subjects had mesangial hypercellularity (M1) in the study.The majority of patients who underwent renal biopsy for microhematuria (66.67%), subnephrotic protienuria (100%), subnephrotic proteinuria with haematuria (92.31%), nephrotic syndrome (50%) and renal insufficiency with proteinuria and haematuria (97.44 %) had M1.

Endocapillary Proliferation

Only minority of patients had endocapillary proliferation (E1) in the study. The E1 was found in 38.46% of subjects with subnephrotic proteinuria with haematuria, 25% with nephrotic syndrome and 17.95% with renal insufficiency with proteinuria and haematuria. None of the subjects with isolated microhematuria orsubnephrotic protienuria had E1.

Segmental Glomerulosclerosis

The segmental glomerulosclerosis (S1) was found 39.68 % in the study. The S1 was found in 33.33% of subjects with isolated microhematuria, 66.67% with subnephrotic protienuria, 23.07 % with

subnephrotic proteinuria with haematuria, 75% with nephrotic syndrome and 48.72% with renal insufficiency with proteinuria and haematuria.

Tubular Atrophy

Tubular atrophy (TA) of grade either T1 or T2 was found in 69.36% of biopsies. The presence of TA was found in 33.33% of subjects with isolated microhematuria, 33.33% with subnephrotic protienuria, 56.16% with subnephrotic proteinuria with haematuria, 50% with nephrotic syndrome and 84.62% with renal insufficiency with proteinuria and haematuria.

Table 1: The demographic data of subjects with IgAN (age)

Gender	N	Mean	Std, Deviation	Std. Error
Females	26	35.96	13.55	2.66
Males	36	38.97	14.73	2.45
Total	62	37.71	14.21	0.95

Table 2: Frequencies of MEST score combinations

• M1 E0 S0 T1: 25.81 %	• M1 E1 S0 T0: 0.3 %
• M1 E0 S0 T0: 9.68 %	• M1 E1 S0 T1: 0.1 %
• M1 E0 S1 T1: 0.1 %	• M1 E1 S0 T2: 6.45 %
• M1 E0 S0 T2: 0.1 %	• M1 E1 S1 T0: 0.1 %
• M1 E0 S1 T0: 9.68 %	• M1 E1 S1 T1: 4.76 %
• M1 E0 S1 T1: 9.68 %	• M1 E1 S1 T2: 0.3 %
• M1 E0 S1 T2: 14.52 %	• M0 E0 S0 T0: 6.45 %

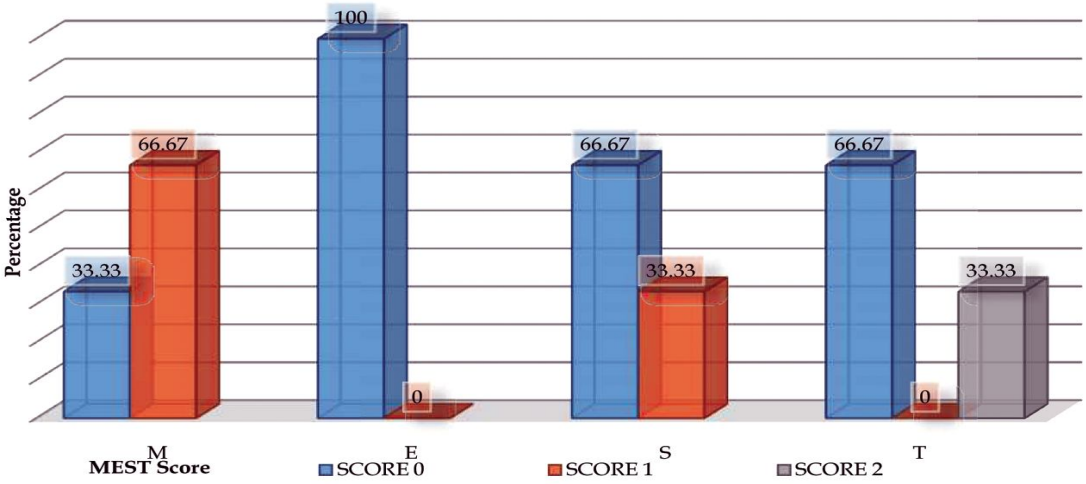


Fig. 1: Mest score in those microhematuria

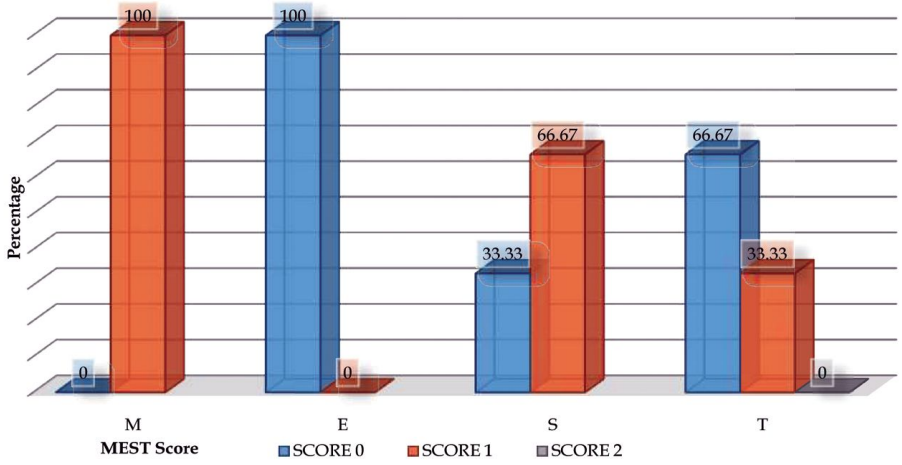


Fig. 2: MEST in those with proteinuria

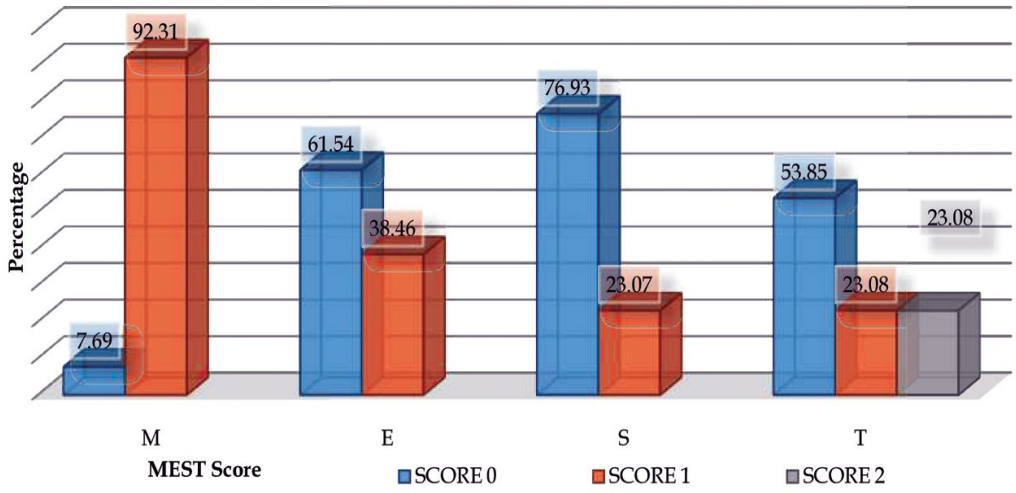


Fig. 3: MEST score in those with protienuria and microhematuria

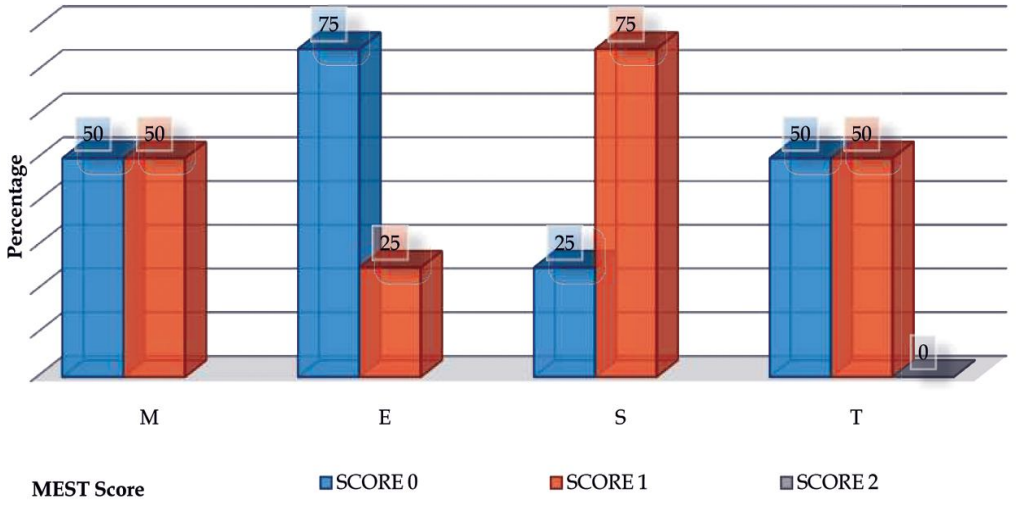


Fig. 4: Mest score in those with nephrotic syndrome

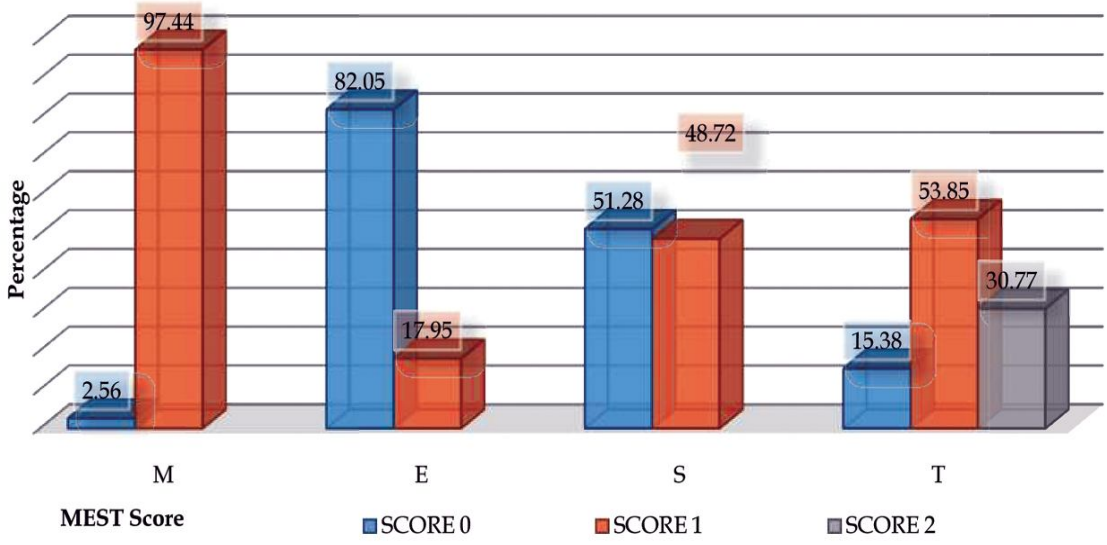
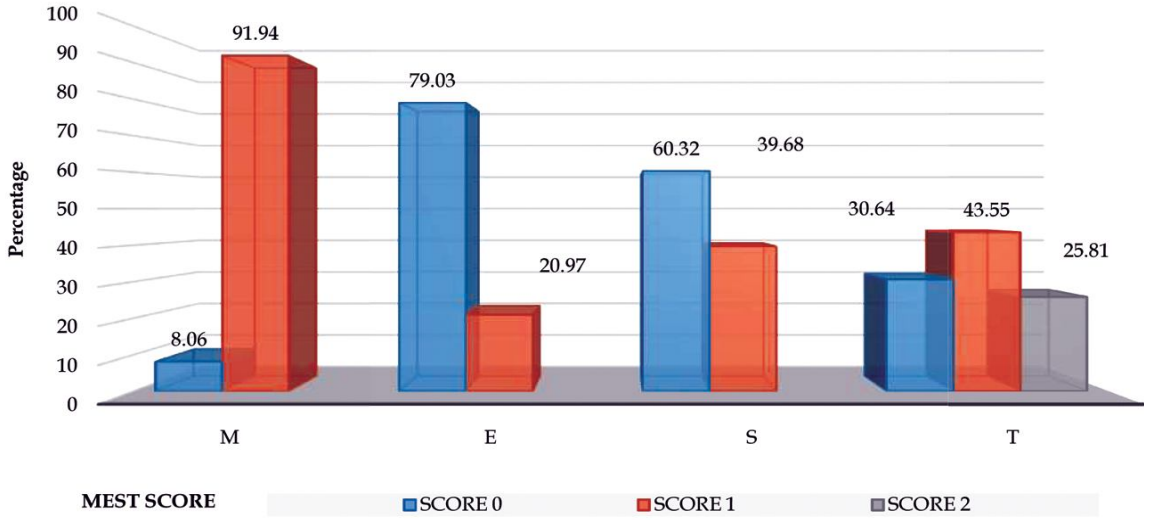


Fig. 5: Mest score in those with Renal Insufficiency



Fug. 6: Mest score of the all subjects study

Discussion

IgAN is among the most common glomerular diseases worldwide, with varying histological patterns [1-6]. Oxford classification of IgAN by MEST scoring, is an important step for classification as it will serve to achieve for uniformity in classification, initiation, monitoring of treatment [7]. It will also aid easier design of multicentre trials and analysis.

In our study the IgAN was the most common biopsy proven renal disease; more common in males than females and majority of the subjects were of age < 40 years. The presence of renal insufficiency with proteinuria and haematuria was the commonest indication for renal biopsy (62.90%) followed by subnephrotic proteinuria with haematuria (20.97%), nephrotic syndrome (6.45%),microhematuria (4.84%) and subnephrotic protienuria in 4.84 % of subjects. Overall prevalence of M1, E1, S1, T1 and T2 was noted in 91.94, 20.97, 39.68, 43.55 and 25.81% of renal biopsies respectively.

In of the earlier studies from India; involving 66 patients (male: female ratio of 4.4:1; mean age: 29.9 years), the prevalence of MEST scores M1, E1, S1, T1 and T2 were observed in 68.18%, 24.24%, 48.48%, 30.30% and 43.93% in respectively [11].

In a study from Iran (102 patients,72% males, mean age: 37.7 ± 13.6 years) the rates MEST variables were; M1: 90.2 %, E: 32 %, S: 67 %, T in grades 1 and 2 were in 30% and 19% respectively [12].

In a Brazilian study (600 patients; Male to female ratio: 1.24:1; mean age of 32.76 ± 15.12 years); M1 and S1 were the main glomerular findings (47.6 and 46.2 %). T1 or T2 was observed in 32.2% of the cases. Segmental sclerosis (S1) showed a stronger tendency of association with the presence of tubulointerstitial lesions (T1 and T2) than other glomerular variables.Tubular atrophy and interstitial fibrosis were more strongly associated with higher 24-h proteinuria and serum creatinine levels [13].

The findings of the present study are consistent with first two studies and patients in Brazilian had milder form of disease with mean serum creatinine level of 1.5 mg/dl with lesser of them having mesangial hypercellularity and tubular atrophy [11, 12, 13].

Most patients in the present study presented with renal failure similar to profile of earlier studies [11, 12] and except that a significant percentage (23%) also had nephrotic range proteinuria in one of them [11]. The present study being a hospital based one, might led to the bias in selection for biopsies towards those with renal insufficiency similar to other studies. [11, 12].

The commonest combinations of MEST scoring in the study were M1, E0, S0, T1 (25.81%), followed by M, E0, S1, T1 (14.52%) and M0, E0, S0, T0, was seen only in 6.45% of cases. Whereas; the commonest combination was M0 E0 S0 T0 (22.4%) in Brazilian study, expectedly as patients had milder form of disease [13].

In the present study, of the MEST variables presence of M1, TA (T1 or T2) had a statistically significant correlation with indication for biopsy on univariate analysis, however; only on TA showed a statistically significant correlation on multivariate analysis. There was no statistically significant effect of gender or age on indication for renal biopsy or MEST score on multivariate analysis.

In one of the earlier study; gender had a significant effect (males > females) was on presence of segmental glomerulosclerosis and interstitial fibrosis/ tubularatrophy. The possible reason for this difference being a higher serum creatinine and protienuria in males in that study [12].

Conclusions

IgAN is more common in males and affects those of younger age.Majority of patients who underwent biopsy had renal insufficiency; majority of those presenting with renal insufficiency had M1 and T1 or T2. Among the MEST score combinations M1 E0 S0 T1, was the commonestand M0 E0 S0 T0 was one the least common patterns, implying a severe disease at presentation in our population. The presence of M1, TA (T1 or T2) had a statistically significant correlation with indication for biopsy on univariate analysis, however; only on TA showed a statistically significant correlation on multivariate analysis. There was no statistically significant effect of gender or age on MEST score on multivariate analysis.

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Case Report

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Primary Carcinoid Tumor of Urinary Bladder: A Rare Case Report and Literature Review

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Abstract

Carcinoid tumors are known to arise from enterochromaffin cells and are usually found arising from tissue derived from the embryonicneural crest. Although they are more commonly encountered in gastrointestinal and respiratory organs, rarely they have also been encountered in the genitourinary tract, including the kidney and urinary bladder. Only 29 cases of pure carcinoid tumor of bladder have been reported so far in the literature.

We report here another case of pure carcinoid tumor of bladder involving the prostatic urethra and whole of the prostate, who underwent radical cystectomy.

Keywords: Primary Carcinoid Tumor; Bladder Carcinoid; Malignant Bladder Carcinoid; Pure Carcinoid of Bladder.

Introduction

Carcinoid tumors commonly occur in gastrointestinal tract and respiratory tract, but carcinoid tumors of the genitourinary system like kidney, urinary bladder, prostate and urethra have also been reported. About 29 cases of primary bladder carcinoid have been reported so far in the literature [1-3]. Carcinoid tumors arise from enterochromaffin cells and arise from tissue derived from embryonicneural crest.These cells are also known as enterochromaffin cells or amine precursor uptake and decarboxylation (APUD) cells.

There are various theories proposed regarding the origin of these carcinoid tumors like origin frommetaplastic bladder urothelium, or presence of enterochromaffin cells in bladder, or arise from neural crest tissue entrapped within the metanephros during embryogenesis, or that they represent metastases from an occult carcinoid tumor elsewhere in the body [4].

In this report, we describe the clinical, histopathologic, and immunophenotypic features of a pure carcinoid tumor of the urinary bladder and review the literature.

Case Report

A 54 year old male was referred to our out-patient departmentwith a history of haematuria since the past 4 months, with passage of clots and intermittent pain during that period. He was a smoker in the past and had no exposure to aniline dyes. He had no significant medical history. His physical examination was normal. He had already undergone CT-Urogram which showed a polypoidal lesion in the right posterolateral wall involving the right

vesicoureteric junction causing right sided hydroureteronephrosis. Also, he had undergone cystoscopy, which revealed a 4cm lesion in the right posterolateral wall and trigone. Biopsy was taken from that lesion and the histopathological report was transitional cell carcinoma of the urinary bladder(GRADE 3). So, he was referred to our hospital for further management.

In view of these findings, radical cystoprostatectomy and dissection of internal iliac group of nodes with ileal conduit was done. The histopathology report was as follows:

- Grossly, it wasulceroproliferative growth in the lower wall of the bladder close to the prostatic urethra measuring 3x2 cms. Tumourwas infiltrating into the prostatic urethra and prostate. There was diffuse thickening of entire wall of bladder more in the lower part. (Figure 1A).
- Microscopically,tumor showed ulcerated mucosa with tumor cells arranged in nesting pattern. Tumor cells were small, monotonous and round, with round, bland nuclei with stippled chromatin and indistinct nucleoli. The nests were separated by septae of vascular tissue (Figure 1B, 1C). Tumor showed muscle invasion and serosa, vascular and perineural invasion. Also, the whole of the prostate was replaced by tumor cells and the tumor extended into the prostatic urethra (Figure 2D). And there was involvement of iliac group of lymphnodes with vessels filled with tumor emboli (Figure 2C).
- Immunohistochemistry study was strongly positive for Neuron Specific Enolase (NSE) (Figure 2B) and Cytokeratin (Figure 2A).

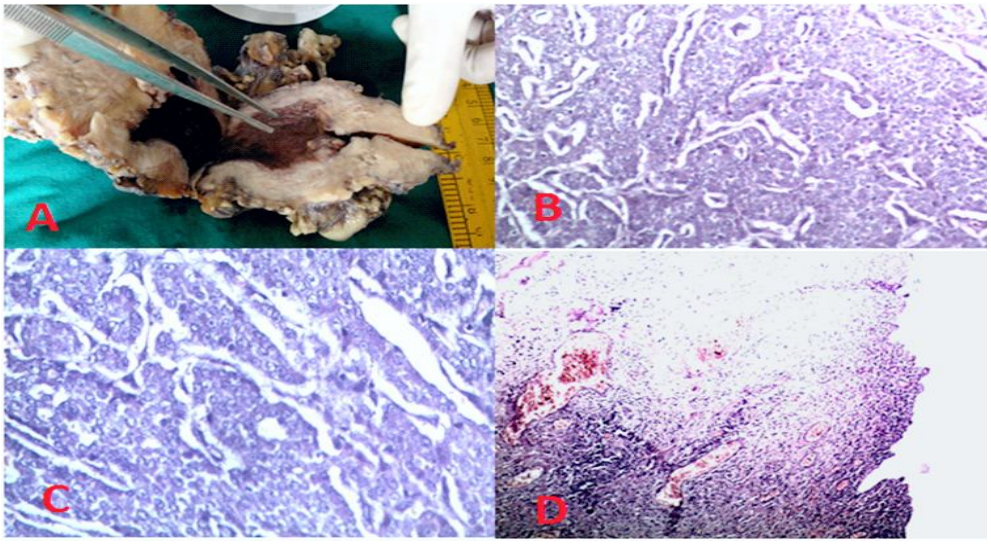

Fig. 1: A–Radical cystectomy specimen cut open to reveal the tumor, B- Monotonous cells arranged in nesting pattern separated by fibrous septae (40X), C- High power view (100X), D- Cystitis with ulceration.

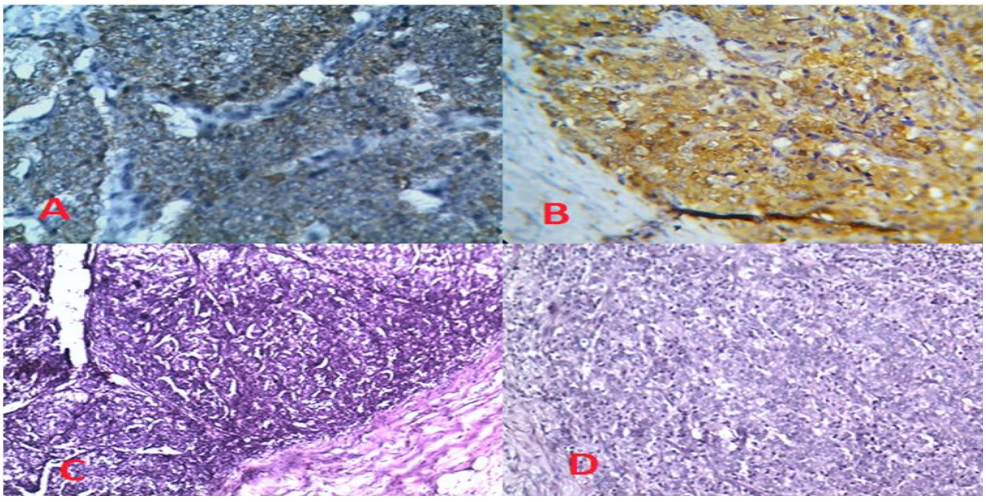

Fig. 2: A-Cytokeratin expression in the tumor, B- Neuron specific enolase expression in the tumor, C- Lymph node showing secondaries, D- Prostatic urethra showing tumor invasion

Thus, it was a carcinoid tumor of the bladder. And as there was no evidence of carcinoid tumors in any other organs, we concluded that this was a case of primary carcinoid tumor of the bladder with invasive nature. There was no element of transitional cell carcinoma found in the specimen.

Discussion

Neuroendocrine tumorscomprise of 1.7% of all bladder tumors [1]. As per the Travis classification, they can be classified into low-grade carcinoid tumors, and high-grade small-cell and large-cell carcinomas [2]. Among these, small cell carcinomas are the most common, with only 29 cases of pure bladder carcinoids reported so far in the literature.

Carcinoid tumors have a variety of growth patterns. On the basis of architecture, they can be classified as insular, trabecular, glandular, undifferentiated, and mixed [5]. Primary bladder carcinoid lesions are mostly seen over trigone or bladder neck and can coexist with other malignancies of bladder as well as inflammatory diseases of the bladder. Usually carcinoid tumours are present submucosally and on cystoscopy appear as polypoid lesions. In all reported cases neuroendocrine differentiation has been readily confirmed by presence of argyrophilic granules or by immunohistochemistry, which reveals presence of chromogranin, synaptophysin, neuron-specificenolaseor other markers of neuroendocrine differentiation.Though carcinoids are slow growing tumors, about 75% of patients have local, distant and / or nodal metastasisat the time of diagnosis [4,6]. Our patient too, had tumor metastasis to the prostate, prostatic urethra and iliac lymph nodes.

As these are very rare tumors, much is not known about their progression and response to various treatment modalities or their long term management.For localizedcarcinoid tumors of the urinary bladder, a variety of treatments have been tried: a multiplebiopsy, transurethral resection, a partial cystectomy, anda total cystectomy or radical cystoprostatectomy depending upon the size of tumor and extent of disease. Many of the reported tumors were small and so were cured by transurethral resection [1].

Not much is known about treatment for metastatic disease, owing to rarity of these tumors. Based upon the studies on neuroendocrine tumors in other parts of the body, two chemotherapy regimens have been recommended: methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) formixed type and cisplatin-etoposide for pure neuroendocrine tumors [7]. But theoverall prognosis of bladder neuroendocrine tumorsremains poor, with a 2-year survival rate of 13%, mostly based on a series ofsmall-cell carcinomas [7].

In view of lack of long term follow-up studies for bladder carcinoids as a consequence of paucity of pure carcinoids cases, the behaviour of these tumors is largely unknown and difficult to predict. Though, size and extent of the lesions usually appear to be most important, and also flow cytometric analysis of DNA ploidy may provide additional prognostic information [8], but nothing can be said conclusively. Mixed carcinoid tumors usually exhibit more aggressive behavior, in line with that expected of the noncarcinoid component [4].

In bladder carcinoids, carcinoid syndrome is not seen due to the fact that the peptides are flushed out of the system in the urine and are not absorbed in the systemic circulation in enough quantities so as to cause symptoms, exception being in cases of metastasis giving rise to large tumour burden, extensive nodal metastasis, or tumours with direct access to systemic circulation.

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Diabetes Mellitus, Chronic Renal Failure & Pulmonary Tuberculosis

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Abstract

Tuberculosis is one of the most common infectious diseases worldwide. Several risk factors including diabetes mellitus, chronic renal failure are known to impair the immunity and are involved in spread of TB. We report a case of diabetes mellitus with chronic renal failure and tuberculosis.

Keywords: Tuberculosis; Diabetes Mellitus; Hemodialysis; ESRD.

Introduction

The first report of the association between diabetes mellitus (DM) and tuberculosis (TB) was documented by Avicenna (980-1027 AD) over one thousand years ago. Since that time, the relationship between DM and TB, and the nature of their interaction with regards to comorbidity have largely been suggested by several epidemiological studies [1]. The World Health Organization began developing guidelines for addressing Tuberculosis (TB) and diabetes (DM) way back in 2009, however the magnitude and importance of this double burden has not quite sunk in even today, among public health practitioners, clinicians and the public.

It is estimated that in 2010 there were 8.8 million (range: 8.5-9.2 million) new cases of TB. On the other hand, TB is the cause of death for approximately two mil- lion people every year [2, 3]. Aging, changes in life style, socioeconomic factors, and population growth have led to an increased prevalence of DM, particularly type 2 DM. The total number of diabetic people worldwide is predicted to rise from 285 million in 2010, accounting for 3.5 million deaths, to 439 million in 2030 [4,5]. Up to 80% of patients with DM live in low income and developing countries [6]. Asia is the epicenter of the growing burden of DM [5] and the largest contribution is from India and China[7].

Chronic renal failure is known to impair immune function and therefore is associated with an increased incidence of TB. Among patients with chronic renal failure requiring renal replacement therapy, rates of TB 10 to 25 fold greater than those in the general population have been reported from the United States, Canada, Europe, and Japan, equating to incidence rates of approximately 250 cases per 100,000 per year [8, 9]. We report a case of a male patient with chronic renal failure and diabetes mellitus, who was diagnosed to have tuberculosis of the lung.

Case Report

A 67 years old male presented to the Urology OPD services with LUTS, breathlessness and uncontrolled

diabetes mellitus. On preliminary laboratory tests, serum creatinine was 9.72 mg%, random blood sugar 301 mg% and serum potassium 6.76 mEq / L. Chest X-ray revealed left sided pleural effusion (Figure 1). Patient was managed by emergency dialysis. The pleural effusion did not subside even after 4 sessions of dialysis. Pleural fluid aspiration was done and its analysis revealed neutrophils 20%, lymphocytes 70%, glucose 371 mg%, LDH 381 U / L and ADA 40 U / L. Pleural fluid PCR (polymerase chain reaction) was positive for TB. A clinical diagnosis of pulmonary tuberculosis was made and patient was put on anti-tubercular treatment.

Patient gradually started to improve. The chest x-rays showed minimal pleural collection. Fever subsided and patients' general condition improved. Patient was also put on maintenance dialysis.

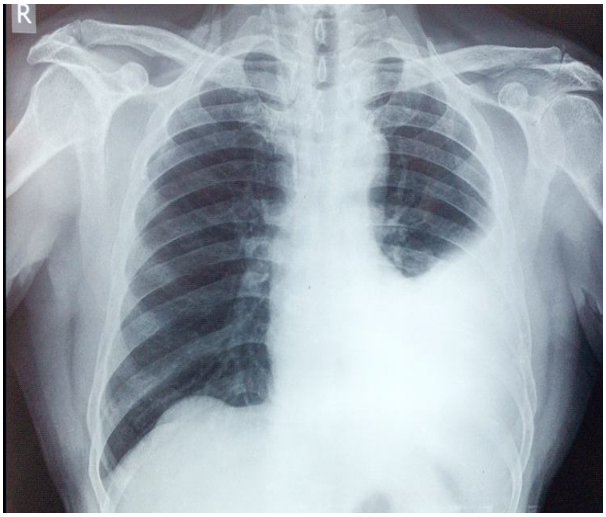

Fig. 1: Chest x-ray revealed left sided pleural effusion.

Discussion

Worldwide, 70% of diabetics live in TB endemic countries. In the 22 countries with the highest burden of TB, the prevalence of DM in the general population ranges from 2% to 9%[5], and eight of the ten countries with the highest incidence of DM are also classified as high burden countries for TB by the World Health Organization (WHO)[10]. China, India, Peru, Indonesia and Russia are the countries that need to be given particular attention[11]. Pulmonary TB is the ninth most frequent complication of DM [12] and due to a rising prevalence of DM, the relative contribution of DM to the TB epidemic is increasing [4,5] . The frequency of DM among active cases of tuberculosis was 5.6%, 7.3% and 14.8% in studies from India, Turkey and Indonesia, respectively. In 35% to 61% of these patients, DM was diagnosed for the first time after detection of TB [13-15].

Chronic kidney disease (CKD) is associated with relative compromise in acquired cell-mediated immunity, which constitutes the major determinant of host resistance for further development of disease. In recent years, the increase in the number of patients with immune suppression, such as those with renal transplantation, has led to increased TB rates in the chronic kidney disease population [16]. The incidence of TB in dialysis patients is higher than in the general population, so screening remains important. Kazancioglu*et al.,* reported that out of 925 Hemodialysis (HD) patients screened from seven different centers, 31 (3.35%) were found to have TB [17].

Our case represents an elderly male with long standing poorly controlled DM and having breathlessness. Evaluation in the hospital revealed chronic renal failure and pulmonary tuberculosis. As reported by the WHO [3], there is abundant evidence of high rates of tuberculosis in patients with DM, and often tuberculosis is only discovered if actively screened / looked for. Strategies to improve health care access, diagnosis, clinical care, financial risk protection, and prevention need to be adapted to this reality. Coordinated efforts for planning and implementation across public health programmes are required.

The sole purpose of this report is to re-emphasize that the world faces a looming co-epidemic of TB-diabetes, and that this is a serious public health risk we all need to urgently address. Physicians of all departments should realize that diabetes makes a person two to three times more likely to develop TB and that the interaction between the two diseases constitutes a worldwide health threat.TB kills more people every year than any other infectious disease except HIV / AIDS. An estimated nine million fell ill with TB in 2013, and 1.5 million died. About one in three people worldwide, an estimated two billion people live with a latent TB infection. In most cases this infection will remain dormant for one's entire life, never making the person sick. However, the risk that this latent infection will progress to active TB disease increases significantly if a person's immune system is compromised for example by diabetes [3,18].

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