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CLINICAL PROFILE AND RESPONSE TO TUBERCULOSIS TREATMENT IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

ORIGINAL RESEARCH ARTICLE

Introduction: Tuberculosis (TB) is a major public health problem, especially in the developing countries Patients with CKD have a weakened immune system due to the chronic inflammatory state due to CKD per se, also due to long term renal replacement therapy. Aims of The Study

1. To study the clinical profile of tuberculosis in chronic kidney disease patients
2. To study the response to anti tubercular treatment including adverse effects.

Methodology: This study was carried out in the Department of Nephrology at Government Stanley Medical College and Hospital, Chennai during the period between October 2018-May 2019. A detailed history was taken, Age, symptomatology, non CKD risk factors like smoking, alcoholism, previous history of pulmonary TB, presence of diabetes mellitus, other infections like HCV, and in case of post-transplant patients, use of induction therapy, any graft dysfunction etc. was noted. The definitions for cure, treatment completed, and treatment failure being used in the study.

Results: There were a total of 55 patients with CKD diagnosed as tuberculosis by various means-clinical, histopathologic, biochemical, microbiologic, radiologic or a combination of factors.

Conclusion: Tuberculosis is a common infection among Chronic Kidney disease patients, due the immunosuppressed state, hence a high

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index of suspicion should be maintained, with ways of early screening to be followed based on clinical grounds. Risk factors, namely, smoking, alcoholism, diabetes mellitus predisposes CKD patients to Tuberculosis in addition to the immunosuppressed state of CKD.

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1. INTRODUCTION

Tuberculosis (TB) is a major public health problem, especially in the developing countries of Asia and Africa. The incidence of Chronic Kidney Disease is increasing due to the changing lifestyle and habits. Patients with CKD have a weakened immune system due to the chronic inflammatory state due to CKD per se, also due to long term renal replacement therapy. Hence they are prone to infectious diseases like tuberculosis. Also due to the same reasons, they may have poor outcomes to treatment.

Patients with renal disease are at increased risk of tuberculosis (TB). This is true for all patients with chronic kidney disease (CKD), 30 times higher prevalence of TB in patients with CRF. The incidence of TB in Indian patients receiving Maintenance Hemodialysis has been reported to be 3.7 to 13.3 percent. Studies showed that 46% of the renal failure patients present adverse reactions to the anti-tuberculosis drugs used, a percentage even higher in dialyzed patients with the same pathology.

Immunodeficiency is a feature of CKD and this is further compounded by immunosuppressive therapy, making these patients more susceptible to reactivation of LTBI or new infection. Identifying patients at risk of TB is not always straightforward, and diagnosing active disease can be delayed as the clinical presentation may be uncharacteristic. Extra pulmonary disease, particularly peritoneal disease, is relatively common and symptoms may be nonspecific. The main difficulties encountered in treating TB in CKD is the risk of adverse reactions of ATT which is more common than in general population, and in post-transplant recipients the drug interaction between immuno-suppressive drugs and Rifampin. Post primary pulmonary tuberculosis may arise in one of three ways: (i) direct progression of a primary lesion; (ii) reactivation of a quiescent primary or post primary lesion; and (iii) exogenous re - infection

Factors contributing to predisposition to tuberculosis include malnutrition, smoking, alcoholism, socioeconomic status, occupation, immunosuppressed states, steroid intake, HIV infection.

The following are the common presentations of tuberculosis:

1. symptom-free, discovered on routine radiography;
2. persistent cough with or without sputum;
3. general malaise;
4. weight loss;
5. recurrent colds;
6. pneumonia which proves to be tuberculous;
7. hemoptysis.

The following characteristics of a chest radiograph favor the diagnosis of tuberculosis:

1. opacities mainly in the upper zone(s);
2. patchy or nodular opacities;
3. presence of a cavity or cavities;
4. presence of calcification;
5. bilateral opacities especially if in upper zones;
6. opacities that persist after several weeks

Chronic Kidney Disease

Chronic kidney disease (CKD) is defined as kidney damage or an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m2 persisting for 3 months or more irrespective of the cause. Kidney Disease Outcomes Quality Initiative (KDOQI)

guidelines have classified CKD into five stages. The Kidney Disease: Improving Global Outcomes (KDIGO) group suggested clarifications including the addition of the suffix *T* for patients with renal allografts and *D* to identify CKD stage 5 patients on dialysis.

The latest 2012 KDIGO CKD classification recommends detailing the cause of CKD and classifying into six categories related to glomerular filtration rate (G1 to G5, with G3 split into 3a and 3b) but also based on three levels of albuminuria (A1, A2, and A3), each assessed according to the urinary albumin-creatinine ratio (in mg/g or mg/mmol in an early morning "spot" urine sample). The term microalbuminuria is no longer incorporated into this classification; the term moderate level of albuminuria is used (30 to 300 mg/g or 2.5 to 30 mg/mmol).The improved classification of CKD has been of benefit to identify prognostic indications related to decreased kidney function as well as increased albuminuria.

2. AIMS OF THE STUDY

1.To study the clinical profile of tuberculosis in chronic kidney disease patients
2.To study the response to anti tubercular treatment including adverse effects
3.To study the pattern of involvement (pulmonary/extra pulmonary) of TB in the same category of patients
4.To study the risk factors of TB in CKD among them

3. REVIEW OF ITERATURE

Tuberculosis is found in high incidence in patients with CKD. There is an estimated 30 times more prevalence of TB in patients with CRF. Compared to general population, patients undergoing dialysis have 10 to 12-fold higher risk of developing TB.

In Indian patients receiving Maintenance Hemodialysis, the incidence of TB is around 3.7 to 13.3 percent. In renal transplant recipients, Incidence of TB has ranged from 1 to 4 % in Northern Europe, 0.5 -1% in North America and around 5 to 10 % in India.

The first infection with the tubercle bacillus is known as primary tuberculosis and usually includes involvement of the draining lymph nodes in addition to the initial lesion (2–4). All lobar segments are at equal risk of being seeded by inhaled infected droplets and in 25% of cases there may be more than one primary focus (5)

Probably within days the infection spreads to regional lymph nodes, with enlargement of hilar, mediastinal or sub carinal nodes. A left-sided pulmonary focus may lead to bilateral adenopathy, whereas right-sided lesions only result in right-sided adenopathy [6]. The combination of the primary (Goon) focus and the draining lymph nodes is known as the primary complex. All other tuberculous lesions are regarded as post primary and are not, at least in whites, accompanied by major involvement of the draining lymph node.

Clinical Features

The main complaints are an insidious onset of symptoms, with fever, anorexia, and loss of weight being which mimics uremic symptoms.

Fever is the main complaint in around 72% of the cases (29–100%), malaise in around 69% (29–100%), and weight loss in around 54% (range 10–100%) as found by Pien et al.

The typical symptoms of TB in the general population like cough and hemoptysis are less commonly reported in dialysis patients (around 22% of cases (5–71%)

4. MATERIALS AND METHODS

This study was carried out in the Department of Nephrology at Government Stanley Medical College and Hospital, Chennai during the period between October 2018-May 2019.This study was ethically approved by the Ethical Committee of Government Stanley Medical College, Chennai. This study is a combined retrospective and prospective one, enrolling 55 cases of Chronic Kidney Disease. The patients

were selected from Nephrology OPD, ward and critical care unit during the study period.

Inclusion Criteria

- CKD patients stage III—V on/not on dialysis
- Renal transplant recipients
- Diagnosed to have tuberculosis by microbiology or histopathology or radiological suspicion

Exclusion Criteria

- Patients not on regular follow up
- Poor drug compliance

Applying all these criteria, 55 Chronic Kidney Disease patients were selected and included in the study after taking their informed consent.

METHODOLOGY

a) Clinical sample and data was collected from -

1. Patients admitted in the Dept. Of Nephrology, Govt. Stanley Hospital with CKD III-V on/not on dialysis or post-transplant recipients
2. Patients with CKD visiting OPD of dept. Of nephrology shall be studied
3. Patients with CKD admitted in critical care unit

b) Method of data collection

A detailed history was taken; Age, symptomatology, non CKD risk factors like smoking, alcoholism, previous history of pulmonary TB, presence of diabetes mellitus, other infections like HCV, and in case of post-transplant patients, use of induction therapy, any graft dysfunction etc. was noted. The patients were grouped into various stages of CKD based on e GFR calculated using the MDRD equation. The diagnostic investigation was noted for each patient with TB – microbiologic / histopathologic / radiologic / newer modalities. The duration of Anti tuberculous therapy taken, adverse drug reactions, if any etc. was noted. The definitions for cure, treatment completed, and treatment failure being used in the study are as follows;

Cured- A patient with pulmonary tuberculosis with bacteriologically confirmed TB at the beginning of treatment who is smear or culture negative in the last month of treatment and on at least one previous testing.

Treatment Completed- A patient with diagnosed tuberculosis who completed treatment without evidence of failure but there is no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because the tests were not done or results not available

Treatment Failure A patient with tuberculosis whose sputum smear or culture is positive at the end of 5 months of ATT or later during treatment.

STATISTICAL ANALYSIS

Collected data was prepared into masterchart in Microsoft Excel and analyzed statistically in SPSS software version 11.5. Results were considered if p value was below 0.05. The collected data were analyzed with IBM.SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis was used for categorical variables and the mean & S.D were used for continuous variables. To find the significance in categorical data Chi-Square test was used. In the above statistical tool, the probability value .05 is considered as significant level**.**

5. RESULTS

There were a total of 55 patients with CKD diagnosed as tuberculosis by various means-clinical, histopathologic, biochemical, microbiologic, radiologic or a combination of factors. The mean age of the study subjects was 40 years .75% of the subjects were males and 25 % females.

Among the risk factors for tuberculosis ,smoking contributed 26 % followed by diabetes mellitus (11%).Majority of smokers among the group developed pulmonary tuberculosis highlighting the association between smoking and pulmonary

tuberculosis.16.4 % of the subjects ,i.e,53 % of the post-transplant subjects received induction therapy with monoclonal antibodies/ antithymocyte globulin .This signifies the fact that immunosuppression caused by these agents, can have a predisposition to the development of tuberculosis.5.5% of the subjects developed graft dysfunction requiring treatment with plasmapheresis /IVIG/ Rituximab /steroids also pointing to the role of predisposition caused by these agents to develop tuberculosis.

CLINICAL FEATURE

Table 1: STAGE OF CKD

		Frequency	Percent
Valid	III	2	3.6
	IV	12	21.8
	V	17	30.9
	Vd	7	12.7
	Vt	17	30.9
	Total	55	100.0

30.9 % of the sample belonged to CKD stage Vt and Vd each respectively, 21.8% to stage IV,12.7% to stage stage Vd and 3.6 % to stage III.

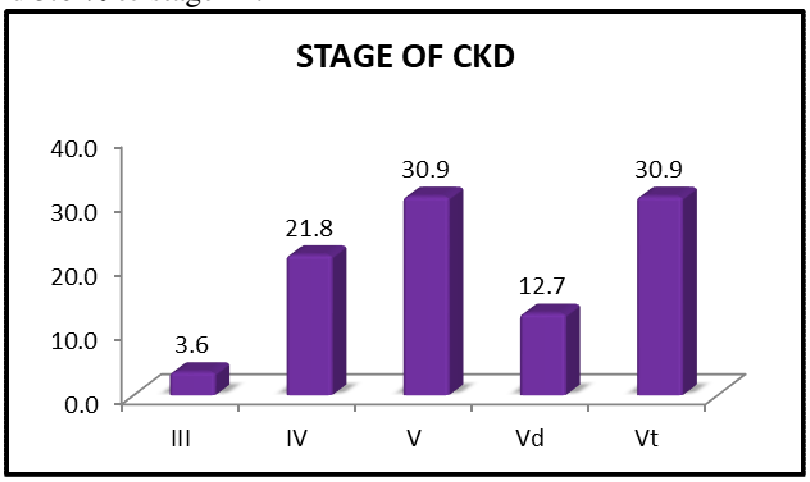

Figure 1: STAGE OF CKD

PULMONARY VS EXTRAPULMONARY

Table 2: TB Distribution

		Frequency	Percent
Valid	P TB	35	63.6
	EP TB	20	36.4
	Total	55	100.0

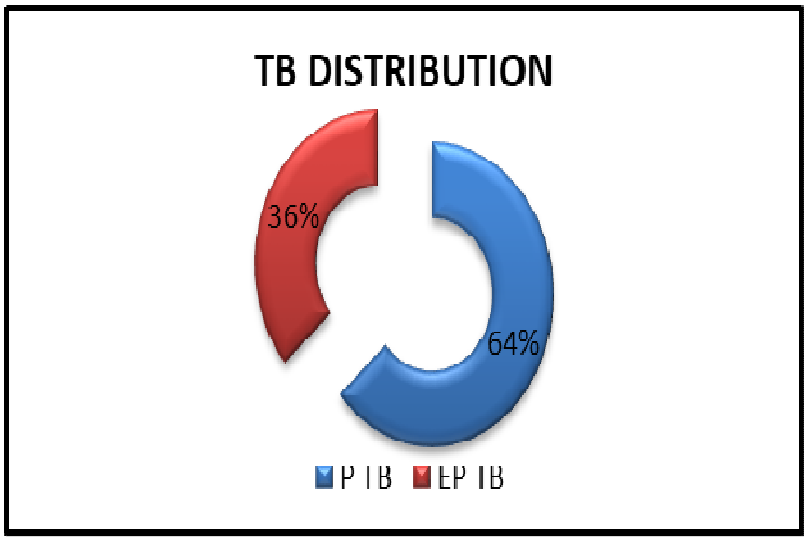

Figure 2: TB Distribution

Of all the patients,64 % had pulmonary TB and 36 % had extra-pulmonary TB

DIAGNOSTIC INVESTIGATIONS

Table 3: Diagnostic Investigations

Diagnostic investigations		Frequency	Percent
	Ascitic fluid AFB+,Bactec MTB +	1	1.8
	aspirate gene xpert+,granuloma+	2	3.6
	BAL MTB +	4	7.3
	CSF gene xpert MTB+	1	1.8
	CT chest	2	3.6
	exudative pleural fluid,high ADA	11	20.0
	FNA LN- granuloma	6	3.6
	high protein CSF , gene xpert MTB+	1	1.8
	LN excision biopsy positive	3	5.5
	MRI spine	4	7.3
	sputum AFB+	13	23.6
	sputum gene xpert	2	3.6
	synovial biopsy	5	7.3
	Total	55	100.0

RESPONSE TO TREATMENT

Table 4: Response to treatment

		Frequency	Percent
Valid	C	18	32.7
	Defaulter	3	5.5
	Pending	5	9.1
	TC	28	50.9
	TF	1	1.8
	Total	55	100.0

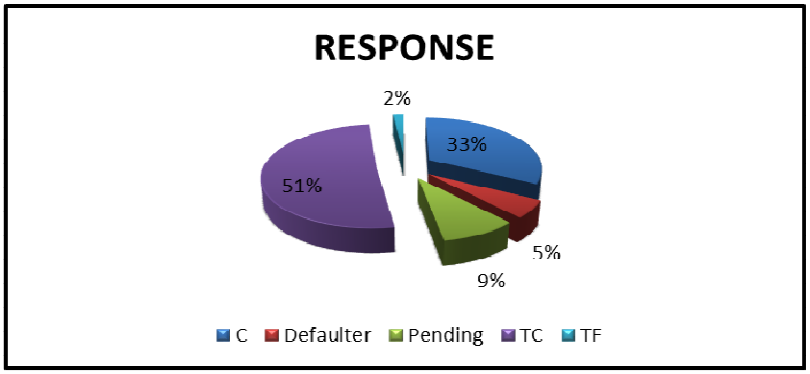

Figure 3: Response

28 % of the patients completed treatment,18 % were declared cured, 5 % were on ongoing treatment, 3% defaulted and 1 % were treatment failed cases.

STAGE OF CKD

Table 5: Stage of CKD

			Pulm(P)/Extrapulm(E)		
			E	P	Total
STAGE OF CKD	III	Count	1	1	2
		P/E	2.9%	5.0%	3.6%
	IV	Count	11	1	12
		P/E	31.4%	5.0%	21.8%
	V	Count	11	6	17
		P/E	31.4%	30.0%	30.9%
	Vd	Count	7	0	7
		P/E	20.0%	0.0%	12.7%
	Vt	Count	5	12	17
		P/E	14.3%	60.0%	30.9%
Total		Count	35	20	55
		P/E	100.0%	100.0%	100.0%

The comparison between Stages of CKD and TB types shows that there is a high statistical significance with ($\chi 2 = 16.84$, df =4, P = 0.002 < 0.01)

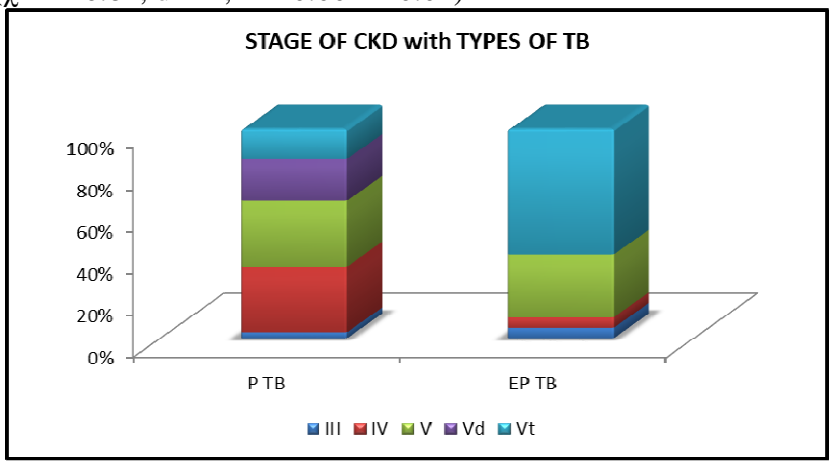

Figure 4: STAGE OF CKD with TYPES OF TB

The relative percentages of pulmonary and extra pulmonary TB were done stage wise and it was found that in case of pulmonary TB maximum percentage of cases were of stage IV and V and in case of extra pulmonary maximum percentage of case were of CKD stage V post-transplant status.

RISK FACTORS

Table 6: Risk factors

		Frequency	Percent
SMOKING	No	41	74.5
	Yes	14	25.5
ALCOHOLISM	No	50	90.9
	Yes	5	9.1
OLD PT	No	52	94.5
	Yes	3	5.5
T2DM	No	49	89.1
	Yes	6	10.9
NODAT	No	53	96.4
	Yes	2	3.6
GRAFT DYSFUNCTION	No	52	94.5
	Yes	3	5.5
HCV POSITIVE	No	53	96.4
	Yes	2	3.6

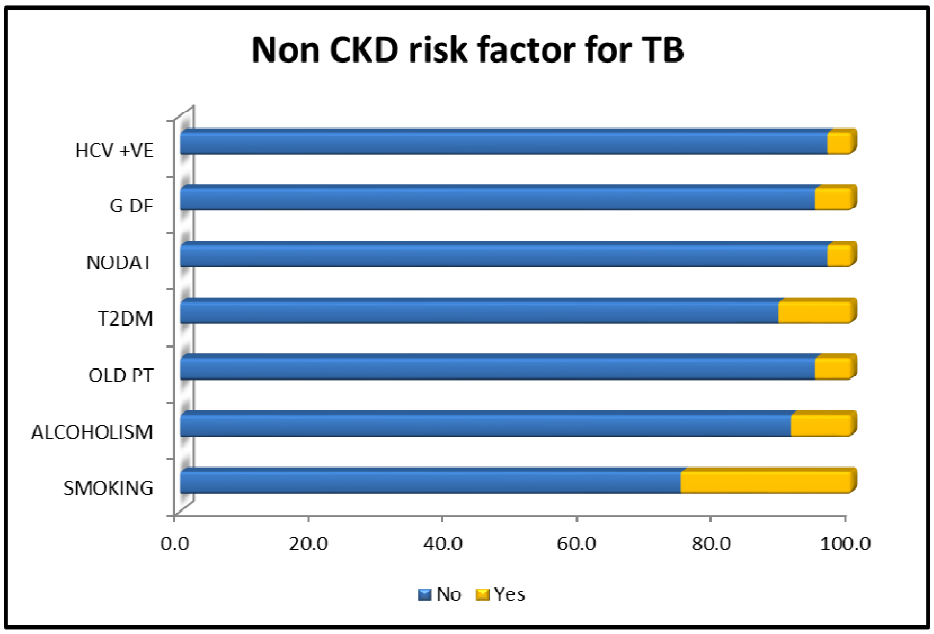

Figure 5: Non CKD risk factor for TB

In the above table Smoking 25.5 % of the patients with TB were smokers as per the study

9.1 % of the patients with TB were alcoholics. 5.5 % of the TB patients had history of prior pulmonary tuberculosis. **10.9** % of the sample had diabetes mellitus. **3.6**% of the population had. New onset diabetes mellitus after transplant. **5.5 %** of the sample had evidence of graft dysfunction. **3.6** % of the population was HCV positive.

7. DISCUSSION

Tuberculosis (TB) is one of the major causes of mortality across the world. Because of the immunosuppressive effect of uremia, patients with chronic kidney disease (CKD) are at high risk of developing TB. There is limited information on the magnitude of the problem of TB in patients with CKD. Aim of the study was to find out the clinical profile, response to treatment of Tuberculosis in CKD patients in Govt. Stanley Medical College, Chennai over a period of 8 months (October 2016-May 2017). There were a total of 55 patients with CKD diagnosed as tuberculosis by various means-clinical, histopathologic, biochemical, microbiologic, radiologic or a combination of factors. Among the risk factors for tuberculosis ,smoking contributed 26 % followed by diabetes mellitus (11%).Majority of smokers among the group developed pulmonary tuberculosis highlighting the association between smoking and pulmonary tuberculosis.16.4 % of the subjects ,i.e,53 % of the post-transplant subjects received induction therapy with monoclonal antibodies/ antithymocyte globulin .This signifies the fact that immunosuppression caused by these agents ,can have a predisposition to the development of tuberculosis.5.5% of the subjects developed graft dysfunction requiring treatment with plasmapheresis /IVIG/ Rituximab /steroids also pointing to the role of predisposition caused by these agents to develop tuberculosis.

In this study, pulmonary tuberculosis contributed 64 % of cases (majority in stages IV and V CKD) and extra pulmonary 36% (maximum number in post renal transplant subjects). Of the latter group, pleural TB topped in number accounting to 20 % of cases followed by skeletal TB, lymph node and abdominal TB, and disseminated TB being least in number.

- The risk factors like smoking, alcoholism, prior TB,T2DM like previous studies remain relevant in present study too. Factors like graft dysfunction, NODAT and HCV positivity too were seen in common in some cases of tuberculosis in post-transplant patients, whether they have any role as a contributing factor to tuberculosis needs further studies to explain.
- Extra pulmonary TB is the major type in CKD stages III,IV,Vd(lymph node TB being the major type) and Pulmonary being the major type in CKD Vt ,in par with studies, namely, Tony et al, Sakhuja et al.
- CNS , skeletal , abdominal, pleural TB doesn't have statistically significant difference in percentage when compared between post-transplant CKD and subjects on dialysis ,in contrast to Tony et al study

8. CONCLUSIONS

- Tuberculosis is a common infection among Chronic Kidney disease patients, due the immunosuppressed state , hence a high index of suspicion should be maintained, with ways of early screening to be followed based on clinical grounds.
- Risk factors, namely, smoking, alcoholism, diabetes mellitus predisposes CKD patients to Tuberculosis in addition to the immunosuppressed state of CKD.
- 3.Gene expert assay is a novel, reliable diagnostic modality for tuberculosis, especially in CKD subjects for whom many of the conventional methods may be negative.
- Bronchialveolar lavage increases the detection rates of AFB.

- Pulmonary TB is more common in post-transplant , whereas extra pulmonary (lymph node) more common in both CKD-HD and CKD- NHD groups.
- The tuberculosis cure rates are reasonably good with timely follow up, monitoring by renal and pulmonary physicians.

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