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ASSOCIATION OF HEMATOLOGICAL AND BIOCHEMICAL ABERRATIONS WITH RIFAMPICIN RESISTANT STATUS IN PATIENTS OF PULMONARY TUBERCULOSIS IN A TERTIARY CARE HOSPITAL OF EASTERN INDIA

Laboratory Medicine

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ABSTRACT

Introduction: Pulmonary tuberculosis is a major health issue in most developing countries including India. The disease is amenable to treatment with anti-tubercular drugs. However, a chief impediment in disease elimination is posed by the phenomenon of development of resistance to the first line anti-tubercular drugs inclusive of Rifampicin. This resistance is also often accompanied by hematological aberrations like anemia and neutrophilia as well as hepatocellular dysfunction manifested by escalating levels of liver enzymes, such aberrations being more profound in the elderly and those with co-morbidities. **Methods:** We conducted a retrospective, analytical, comparative audit in the Department of Laboratory Medicine of CK-Birla Hospitals, CMRI & BM Birla Heart Research Centre, Kolkata, from 1st January 2023 to 31st December 2025, utilizing 153 broncho-alveolar lavage [BAL] fluid samples, in diagnosed cases of pulmonary tuberculosis, admitted into the in-patient department and intensive care unit of the hospital with respiratory symptoms. The Rifampicin resistant Mycobacterium tuberculosis bacteria were quantified using the CBNAAT technology and the degree of resistance detected was further sub-categorized as per a scoring system. These scores were further utilized for assessing the extent of concurrence with selected hematological and biochemical parameters, that are known to be raised in the setting of multi-drug-resistant TB. The data was analyzed by GraphPad Prism (v.8.4.3) and MS Excel 2013, considering a p value of ≤ 0.05 to be statistically significant. **Results:** Out of the total 153 BAL fluid 136 were found to exhibit Rifampicin resistance but to varying degrees. A numerical score, of 20, 15, 10, 5 and 0 were assigned for very high resistance, high resistance, medium resistance, low resistance and undetected resistance, respectively. The percentages in each category were calculated. Furthermore, the different categories of Rifampicin resistant M tuberculosis were compared with selected hematological [blood hemoglobin, differential neutrophil & lymphocyte counts and ESR] and biochemical [serum ALT & AST] parameters. A significant association was found to exist between Rifampicin resistant bacterial load and the selected parameters [$P < 0.0001$]. **Conclusions:** Rifampicin resistant Mycobacterium tuberculosis, is a common phenomenon particularly among hospital admitted patients of pulmonary tuberculosis. Such drug resistance is also accompanied by significant hematological and biochemical aberrations chiefly in the form of anemia, neutrophilia, inflammation and hepatocellular dysfunction, all of which often become contributory to an overall poor health outcome for such individuals.

KEYWORDS

Mycobacterium Tuberculosis, Rifampicin, Multi-Drug Resistance

INTRODUCTION

Tuberculosis (TB) remains a major cause of global health problem with an annual incidence of around 10 million people continuing to fall prey to the disease and with more than 1 million deaths, making it the world's leading cause of death from a single infectious agent and among the top 10 causes of death worldwide.[1] An estimated 25% of the annual load of TB cases is attributable to India and with around 50% of the multi-drug resistant [MDR] TB cases and 28% of global mortality can be traced back to this country. [2] As part of comprehensive therapy plan, the directly observed treatment short-course [DOTS] as per the World Health Organization [WHO], constitutes standard for treatment of tuberculosis disease, with the revised national tuberculosis control program [RNTCP], being formulated in accordance with this treatment regime. The program launched in India in 1997, and expanded pan India in a phased manner, to attain a nation-wide coverage as of March 2006, is currently known as the national tuberculosis elimination program [NTEP]; a flagship public health initiative, launched in 2020, with the aim to completely eliminate TB by 2025. [1,3,4] An integral part of the above drug regime involves administration of Rifampicin as a first-line antitubercular drug [ATD]. This drug along with Isoniazid, constitute the primary first-line ATDs. Resistance to both these drugs defined as multi-drug resistance [MDR], with or without resistance to other drugs.[5] According to the 2024 reports by WHO, globally, about 3.2% of new cases and 16% of chronic MDR TB cases had already received therapy, with this number equating to almost half a million new cases of MDR.TB with rifampicin resistance [MDR/RR.TB]. [6]

A "presumptive case of MDR-TB" is defined as a TB patient who fails new treatment regimen and retreatment regimens with first-line anti-TB drugs, who is sputum smear positive at the end of the 4th month of treatment or later and close contacts of drug-resistant TB cases. [7] The persistence of MDR is known to have serious adverse impact on the hematopoietic machinery affecting both marrow as well as peripheral blood pictures. A wide spectrum of hematological abnormalities can manifest inclusive of anemia, leukocytosis, leucopenia, neutrophilia, lymphopenia, thrombocytosis, and thrombocytopenia, all of which are of significantly more pronounced severity in immunocompromised state, namely in individuals co.infected with Human Immunodeficiency Virus [HIV]. [8] Among the hematological aberrations, anemia [9] and neutrophilia [10] are known to predominate, these being more problematic in critically ill patients and often acting as harbingers of frank sepsis in such individuals. [11]

Another common organ to be affected in MDR TB is the liver, with hepatotoxicity manifesting as hepatitis (hepatocellular necrosis), cholestasis (impairment of bile flow), and zonal necrosis.[12] Rates of hepatotoxicity are known to vary from 1% to as high as 80%, in patients with MDR TB particularly those with MDR/RR-TB.[13] The liver transaminases namely alanine aminotransferase [ALT] and aspartate aminotransferase [AST] are traditionally considered to be reliable biomarkers of hepatocellular function, with high enzyme activities heralding hepatocellular dysfunction, particularly in the setting of concomitant existence of comorbidities and in the geriatric population. [14] Infact, monitoring liver enzyme activities is critical in

the therapeutic management of TB due to the potential risk of drug-induced liver injury [DILI], with early detection of elevated liver enzymes allowing for timely dose adjustment or substitution with less hepatotoxic drugs, thereby preventing the progression of liver injury. Such surveillance is particularly vital because symptoms of liver injury are often subtle and progression remains undetected until late. [15] Our current study involved a retrospective audit of the load of MDR-TB bacteria [Rifampicin resistant; RR] in 153 broncho-alveolar lavage [BAL] fluid samples, among diagnosed cases of pulmonary tuberculosis; the gene targeted being the one responsible for resistance to Rifampicin. In parallel the values of corresponding hematological parameters namely, blood hemoglobin, differential counts of neutrophils & lymphocytes and erythrocyte sedimentation rate [ESR] and liver function test parameters namely, serum ALT and AST, were recorded and compared with the concomitant load of Rifampicin resistant TB.

MATERIALS AND METHODS

Study Variables: A retrospective, analytical, comparative audit was conducted in the Department of Laboratory Medicine of CK-Birla Hospitals, CMRI & BM Birla Heart Research Centre, Kolkata, from 1st January 2023 to 31st December 2025, utilizing 153 broncho-alveolar lavage [BAL] fluid samples, in diagnosed cases of pulmonary tuberculosis, admitted into the inpatient department and intensive care unit of the hospital with respiratory symptoms.

Case Selection and Sampling Details: Briefly, 153 BAL fluid samples belonging to patients with pulmonary tuberculosis, admitted into the inpatient department and intensive care unit of the hospital with respiratory symptoms, were selected, in whom Rifampicin resistance had been detected, as part of their treatment work-up plan. Along with the reports of this drug resistance, the reports of selected hematological and hepatic aberrations, were also taken into consideration for the audit process.

Ethical Considerations: Since the entire study was conducted on samples of patients, coming to lab for routine investigations, hence ethical clearance was not required separately for the same.

Detection of Rifampicin resistance and scoring of extent of resistance: The 153 BAL fluid samples were tested for presence of Rifampicin resistant Mycobacterium tuberculosis, using the Cartridge-Based Nucleic Acid Amplification Test [CBNAAT], via the GeneXpert platform, Cepheid Inc; a rapid, automated molecular test that detects Mycobacterium tuberculosis DNA and Rifampicin resistance, delivering accurate results in under two hours, acting as a crucial diagnostic tool for active TB and drug-resistant TB, under the NTEP guidelines. The results of the CBNAAT which is a real-time [quantitative] polymerase chain reaction [qPCR] to detect rifampicin resistance (marker for drug resistance) and TB bacteria in a single, automated step; were further segregated into those with very high resistance, high resistance, medium resistance, low resistance and undetected resistance. Each segment was assigned a numerical score, this being 20, 15, 10, 5 and 0 for very high resistance, high resistance, medium resistance, low resistance and undetected resistance, respectively.

Hematological and Biochemical Analyses: Among the hematological parameters chosen for the study, were blood hemoglobin, differential counts of neutrophils & leucocytes and erythrocyte sedimentation rate [ESR]. The blood hemoglobin was estimated using an automated, cyanide-free spectro-photometric method. The cellular components ie the total leucocyte count [TLC] and the differential percentages of neutrophils and lymphocytes were quantified by Coulter principle & flow cytometric analysis. ESR was estimated manually by the Westergren method. Excepting ESR, all other hematological analyses were carried out using an automated platform viz; HORIBA ABX Pentra XL 80.

The biochemical markers selected were liver function test parameters, namely serum ALT and AST, whose activities were assayed on automated platform, the Roche COBAS c501, using the IFCC recommended methods viz; UV with L-alanine, 2-oxoglutarate, NADH & LDH [Lactate dehydrogenase] and UV with L-aspartate, 2-oxoglutarate, NADH & MDH [Malate dehydrogenase], respectively.

Statistical analyses: The data generated was analysed by MS Excel 2013 and Graph-Pad Prism v.8.4.3, using appropriate statistical tools. Normality of the sample distribution was tested by D'Agostino & Pearson omnibus normality test. To assess the concurrence of selected hematological parameter levels with extent of Rifampicin resistant bacterial quantum, ordinary one-way analysis of variance [ANOVA] was applied [since data was found to be parametric in distribution]. To assess the concurrence of selected biochemical parameter levels with extent of Rifampicin resistant bacterial quantum, Kruskal-Wallis Test was applied [since data was found to be non-parametric in distribution]. In all statistical analysis P value ≤ 0.05, was considered as statistically significant.

RESULTS:

1. **Detection of Rifampicin Resistance and Scoring of Extent of Resistance:** Out of the 153 BAL fluid samples considered, 136 were found to exhibit Rifampicin resistance but to varying degrees. A numerical score, of 20, 15, 10, 5 and 0 were assigned for very high resistance, high resistance, medium resistance, low resistance and undetected resistance, respectively. In brief, out of 153, 41 [27%] exhibited a score of 20, 35 [23%] a score of 15, 49 [32%] a score of 10 and 11 [7%] a score of 5. In 17 [11%] out of the 154 BAL fluid samples, Rifampicin resistant M. tuberculosis remained undetected and hence was designated a score of 0. Figure 1 summarises the scoring distribution of Rifampicin resistant M tuberculosis detected in BAL fluid, along with the respective percentages of the same.
2. **Concurrence of Selected Biochemical and Hematological Biomarker Levels with Quantum of Rifampicin Resistant Bacterial Load:** For assessing the concurrence of our selected hematological parameter levels with extent of Rifampicin resistant bacterial quantum, ordinary one-way analysis of variance [ANOVA] was applied [since data was found to be parametric in distribution]. To assess the concurrence of selected biochemical parameter levels with extent of Rifampicin resistant bacterial quantum, Kruskal-Wallis Test was applied [since data was found to be non-parametric in distribution]. The one-way ANOVA showed a significant concurrence between Rifampicin resistant bacterial load and hematological parameters namely blood hemoglobin, differential counts of neutrophils & lymphocytes and ESR [$P < 0.0001$; Figure 2]. The Kruskal-Wallis Test too exhibited a significant concurrence between Rifampicin resistant bacterial load and selected biochemical parameters namely serum ALT and AST [$P < 0.0001$; Figure 3].

DISCUSSION

Tuberculosis continues to pose a significant health hazard globally, with a high magnitude of mortality and morbidity continuing to prevail in the developing world in particular. [1, 16] The advent of resistance to first line antitubercular drugs adds to the existing challenges in a significant fashion. This has a serious repercussion not only on elimination of the bacteria but also on various body systems, both of which contribute towards a worse patient outcome. [17]

In particular, the tubercle bacillus is known to significantly affect the cellular mileau of the bone marrow often leading to pan suppression of marrow haematopoiesis.[9] Anemia in particular is a common phenomenon with a normocytic normochromic peripheral blood picture. Several studies have reported prevalence of anemia to the tune of 20-94%. [18, 19, 20] In our study 62 out of the 153 samples analyzed [41%], presented with normocytic normochromic anemia [blood hemoglobin level <11.0 g/dL]. The primary driving force behind this anemia appears to be a deluge of pro.inflammatory cytokines, such as IL.6 and TNF.α, which disrupt erythropoiesis through several mechanisms including reduced erythropoietin [EPO] production, suppression of bone marrow response to EPO, and dysregulated iron metabolism. [21,22]

Another interesting phenomenon, observed in drug resistant TB, is the concomitant existence of differential leucocytosis and leucopenia. This is manifested primarily by co-existing neutrophilia and lymphopenia. The chief reason behind high neutrophil count is significant recruitment of the same by phagocytic cells, in response to the bacterial onslaught. [23] Our study showed presence of neutrophilia [differential count >75%] in 79 of the 153 obtained samples accounting for 52% ie majority of samples.

In contrast lymphopenia [differential count <20%] was observed in majority of the collected samples [88 out of 153; 57.5%]. The main underlying mechanism behind this seems to be the immuno-

modulatory effect exerted by alveolar macrophages that selectively inhibit the proliferation of T cells but permit T cell activation and effector functions such as cytokine secretion within the lungs. [24] Other mechanisms include, activation-induced cell death [AICD] in T lymphocytes, which is triggered by the death receptor and results in apoptosis, [25, 26] M. tuberculosis triggered apoptosis that leads to often drastic drops in absolute counts of CD4+ & CD8+ T-lymphocytes, [27,28] as well as differential stimulation of hematopoietic stem cells [HSCs], leading to waxing of myelopoiesis and waning of lymphopoiesis. [29, 30] The last was possibly the attributable cause behind the co-existent neutrophilia and lymphopenia in our sampled population.

Another problematic scenario is that of hepatocellular dysfunction, commonly seen in patients of pulmonary TB, particularly those exhibiting resistance to first line ATDs namely Rifampicin. This drug itself is known to be potentially hepatotoxic and considered to be a prominent agent for causing drug-induced liver injury [DILI], ranging from mild enzyme elevations to, rarely, severe hepatitis or liver failure. [15] It is often used with isoniazid (INH), which increases hepatotoxicity risk, though Rifampicin itself acts as a potent enzyme inducer that can exacerbate liver damage, particularly when used in combination therapies. [31]

Our study showed escalated hepatocellular enzyme activity [> 50 U/L] in 27.5% [42/153] and 26.8% [41/153] of the samples collected. Although not a threatening picture, systematic follow-up liver function assessment is warranted in such individuals as the drug toxicity is cumulative and often associated with elaboration of reactive oxygen species [ROS] which in turn stimulate nuclear factor-κB (NF-κB) inhibitory protein (IκB) to undergo phosphorylation and ubiquitination for degradation, exposing the nuclear localization sequence. The activated NF-κB subsequently is known to translocate into the nucleus, for binding to the same and thereby initiating the expression of pro-inflammatory cytokines viz; TNF-α and IL-1β, among others, which in turn initiate inflammatory cascade and destruction of hepatocytes. [32]

The crucial finding in our study was the highly significant association between the quantum of Rifampicin resistant M. tuberculosis and our selected hematological and biochemical parameters. In both instances, one way ANOVA and its non-parametric counterpart ie the Kruskal-Wallis tests yielded highly significant associations [$P < 0.0001$] between quantum of Rifampicin resistant bacteria and the selected parameters. One of these parameters consciously chosen was the ESR, which too like the other chosen biomarkers, showed highly significant association with quantum of resistant bacterial load. A big chunk of our samples [97/153; 63.4%], exhibited raised ESR [> 30mm /hour]. An important reason for this, lies in the fact that pulmonary tuberculosis infection is commonly accompanied with raised levels of fibrinogen and plasma globulins which are common acute phase reactants [APRs] causing ESR values to rise. [33] Moreover values are known to correlate well with that of C-reactive protein [CRP], a well-established marker of acute inflammation, as well as with levels of pro-inflammatory cytokines namely IL-1β and IL-18, all of which are associated often with a significantly worse prognosis. [34]

CONCLUSIONS

Rifampicin resistant Mycobacterium tuberculosis, is a common phenomenon particularly among hospital admitted patients of pulmonary tuberculosis. Such drug resistance is also accompanied by significant hematological and biochemical aberrations chiefly in the form of anemia, neutrophilia, inflammation and hepatocellular dysfunction, all of which often become contributory to an overall poor health outcome for such individuals. The current study underlines the necessity of identifying such drug resistance as early as possible so that alternative therapeutic strategies can be implemented without delay.

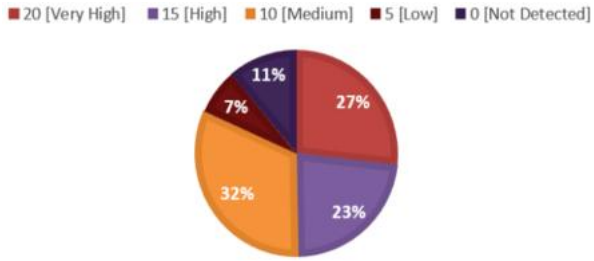

Figure 1: Percentage of Multi Drug Resistant Mycobacterium tuberculosis load in broncho-alveolar lavage [BAL] fluid of pulmonary TB patients [Scoring system; 20= Very high load; 15= High load; 10= Medium load; 5= Low load; 0= Not detected]

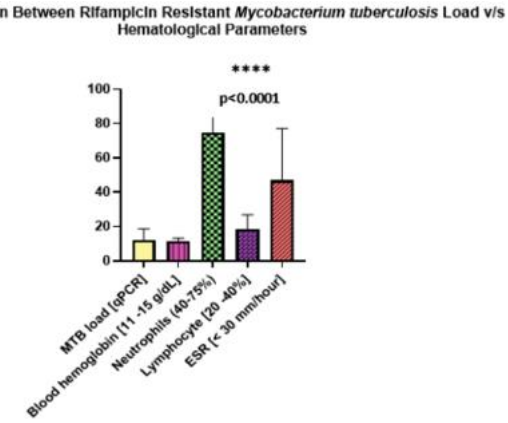

Figure 2: Comparison between Rifampicin resistant Mycobacterium tuberculosis load v/s hematological parameters; Parameters considered blood hemoglobin level [g/dL]; differential neutrophil count [%]; differential lymphocyte count [%] and erythrocyte sedimentation rate [mm/hour]. One way-ANOVA test applied; concurrence between tested parameters highly significant [P<0.0001].

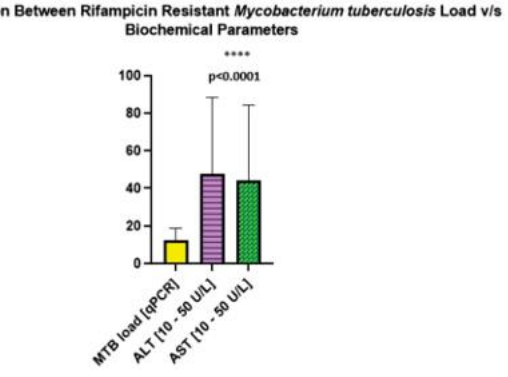

Figure 3: Comparison between Rifampicin resistant Mycobacterium tuberculosis load v/s biochemical parameters; Parameters considered serum ALT U/L] and AST [U/L]. Kruskal-Wallis test applied; concurrence between tested parameters highly significant [P<0.0001].

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