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A PROSPECTIVE STUDY TO OBSERVE THE PREVALENCE AND NATURAL FATE OF IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS) IN HUMAN IMMUNODEFICIENCY VIRUS (HIV)NEGATIVE PATIENTS OF EXTRA PULMONARY TUBERCULOSIS(EPTB)

Medical Science

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ABSTRACT

Objective: Occurrence of Immune reconstitution inflammatory syndrome (IRIS)/Paradoxical reaction (PR) in patients of tuberculosis is a source of diagnostic dilemma to the clinician and is sometimes confused with drug resistance. The objectives of this research were to observe the prevalence and study the natural fate of IRIS/PR in patients of HIV negative EPTB.

Material and Methods: A single centre prospective observational study was conducted at King George's Medical University, Lucknow, India over a period of 18 months (June2016-December 2017) and HIV negative patients of EPTB who were on anti-tubercular treatment(ATT) were followed and observed for various PR which resulted due to immune reconstitution phenomenon.

Results: 324 subjects of EPTB who were on Anti tubercular therapy (ATT) were recruited for the study. Out of these, 56 (17.3%) patients reported with paradoxical reactions. Most commonly encountered paradoxical reaction was appearance of new lymph nodes which was observed in 34 patients (60.7%) followed by enlargement of existing lymph nodes/cold abscess which was seen in 15 (26.7%) patients, paradoxical reaction in the form of pleural effusion was observed in 7 patients (12.5%), involvement of pericardium was observed in 1 patient (1.78%). Most of the IRIS manifestations occurred during the first quarter of ATT (95%).

Conclusion: IRIS was uncommonly seen (17.3%) in patients of extra pulmonary tuberculosis. It was observed that the IRIS manifestations resolved during the course of treatment in 42 (75%) without any intervention except that the treatment was prolonged, 14 patients (25%) however required some form of treatment.

KEYWORDS

Extra pulmonary tuberculosis, Paradoxical Reaction

INTRODUCTION

Immune reconstitution inflammatory syndrome also known as paradoxical reaction refers to appearance of new lesions or aggravation of already existing lesions during anti tubercular treatment [1]. This phenomenon though being uncommon is of importance because it poses diagnostic dilemma to the treating physician and creates unnecessary confusion for drug resistance. IRIS is more commonly observed in patients of extra pulmonary tuberculosis in comparison to pulmonary tuberculosis. This study was undertaken with the intent of bringing more clarity and awareness about this uncommon phenomenon.

MATERIAL AND METHODS

A single center prospective observational study was conducted at King George's Medical University, Lucknow, India over a period of 18 months (June 2016-December 2017). Patients of EPTB who were HIV negative and taking ATT were enrolled for the study. In total 324 patients including 142 male and 182 female subjects were enrolled. Patients were followed and observed for various Paradoxical reactions as a result of immune reconstitution phenomenon.

Inclusion Criteria

- Patients of HIV negative EPTB

Exclusion Criteria

- HIV Positive Patients
- Patients with coexisting pulmonary tuberculosis
- Diabetes Mellitus

The data was compared using Chi square test. Statistical package for social sciences (SPSS V.25) was used to analyze the data. A 'p' value of <0.05 indicated a statistically significant association.

OBSERVATIONS AND RESULTS

Out of the total 324 subjects enrolled for the study,56(17.3%) patients developed paradoxical reactions. The most common paradoxical reaction was appearance of new lymph nodes which was observed in 34 patients (60.7%), the next common PR was increase in size of preexisting lymph nodes/cold abscess which was seen in 15(26.7%) patients, pleural effusion as PR was encountered in 7 patients(12.5%), pericardial effusion was also observed in 1 patient (1.78%). Most of the IRIS/PR occurred during the first quarter of ATT i.e. in 95%.

Table 1- Distribution of patients of EPTB. Tubercular lymphadenitis was reported more in female subjects (p=0.037).

Distribution of EPTB patients	Male	Female	Total
Tubercular Lymphadenitis	108	147	255(78.7%)
Pleural effusion	36	23	59 (18.2%)
Abdominal Tuberculosis	1	3	4 (1.23%)
Pericardial Effusion	4	2	6 (1.85%)
Total			324

Table 2- Patients who reported with PR. There was no significant gender difference in patients reporting IRIS (p =0.447).

	Male	Female	Total
Lymph Node	21(43.7%)	27(56.2%)	48
Pleural effusion	2(28.5%)	5(71.4%)	7
Mediastinal lymphadenopathy + Pericardial effusion	0	1	1

Table 3- Patients in whom IRIS manifestations resolved spontaneously. Intervention was required more often in patients of pleural effusion (p=0.002).

	Lymph Node	Pleural effusion	Mediastinal lymp hadenopathy + Pericardial effusion	Total

Spontaneous resolution	40	2	0	42(75%)
Intervention required	8	5	1	14(25%)

DISCUSSION

Treatment of tuberculosis sometimes incites an inflammatory response which is commonly called as paradoxical reaction. It may manifest as appearance of new lesions or worsening of previously existing lesions, it is a diagnosis of exclusion ruling out disease relapse, failure or alternative diagnosis [2]. HIV co-infection is a known risk factor for paradoxical reaction which is termed as Immune reconstitution inflammatory syndrome (IRIS) however both the terms are used interchangeably at many places. IRIS usually occurs when concomitant anti-retroviral therapy is started [3]. Referring to occurrence of paradoxical reaction in tuberculosis school of thoughts are of opinion that as tuberculosis itself is immunomodulatory so initiation of anti-tubercular treatment can also reverse immune dysregulation as happens in HIV also[4]. However the exact mechanism of this phenomenon is still unclear and one of the proposed mechanism is that dying mycobacteria as a result of ATT release tuberculoproteins and incite an enhanced focal immune response as a result of hypersensitivity which recruits lymphocytes and macrophages at the existing but dormant tuberculosis foci which enlarge and become evident [2]. Evidence of diversity of immune response according to different ethnicity has been also reported in literature [5]. Certain allergic medications have been also reported to result in PR [6].Role of Interleukin-6 and Tumor Necrosis factor α (TNF- α) [7] and other chemokines and cytokines [8] have been recognized but still lacunae exists in proper understanding of this phenomenon. The present study conducted by us was carried out with recruitment of HIV negative cases of extra pulmonary tuberculosis (EPTB) as PR has been reported more frequently in them as compared to pulmonary tuberculosis. The importance of this phenomenon in our context is that the treating doctor often confuses it with treatment failure or resistance and there is an unnecessary modification in the regimen so it is important to keep this in mind to diligently differentiate between PR and other possibilities. Our study demonstrated spontaneous resolution of PR in a major chunk of cases i.e. in 75% of cases who suffered from PR manifestations however it was also seen that patients who developed pus or fluid collection required active intervention in most of them. The most common PR observed was of appearance of new lymph nodes, interestingly we also found a case with paradoxical reaction in form of pericardial effusion with mediastinal lymphadenopathy, a similar case has been reported by Saurabh Karmakar etal [9]. It is worth mentioning here that IRIS is reported much less frequently in non HIV patients as compared to HIV positive patients [10]. There has been evidence in the available literature that baseline C-Reactive protein is associated with risk of developing PR, however it requires larger studies to establish this association [11,12].Erythrocyte sedimentation rate(ESR), which is more than baseline generally in tuberculosis may also prove to be a predictive marker for PR ,however this too requires further work to determine any association[13,14].Our findings suggest that peripheral lymph node disease greatly predisposes to PR. This has been previously documented as a likely site of IRIS. One of the few other important studies in context to our research is the third British Thoracic Society lymph node study which was carried out during 1987-89 on a South Asian cohort in which patients were largely without HIV co-infection, in 16 % of patients within the first three months of treatment new lymphadenopathy was reported [15], and new nodes or sinuses appeared in 7–12 % after completion of treatment [16].

CONCLUSION

Few relevant conclusions were drawn from the present study like possibility of occurrence of paradoxical reaction should always be kept in mind whenever the treating physician encounters worsening of lesions or development of new lesions while treating a case of tuberculosis and treatment failure or resistance should be established after ruling out IRIS/PR. Secondly, the treatment approach should be conservative for IRIS/PR with proper explanation and assurance to the patient as many of the cases are self-limiting although some patients may require some form of intervention along with short term corticosteroids. In our studyIRIS was seen in 17% of patients. IRIS manifestations resolved in 42 patients (75%) without any intervention except that the treatment wasprolonged,14 patients(25%) however required some form of treatment inthe form of pleural fluid aspiration, pus drainage and corticosteroid use.

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Conflict of Interest-

There are no conflict of Interest to disclose.

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