A case of non-HIV related IRIS in a child with MDR miliary CNS TB

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Abstract : TB associated IRIS is commonly associated with treatment of HIV-positive patients. This phenomenon can also occur in non-HIV TB treated patients. It must be suspected in a child worsening while on TB treatment. It presents as new or worsening constitutional symptoms, new or enlarging TB lesions. Here we report an 8 year old child with CNS TB who developed IRIS during treatment.

Key word : TB IRIS, non-HIV, CNS TB, Pediatric, Miliary

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I Introduction:
Paradoxical response to treatment in tuberculosis is well known to occur in HIV positive patients. The incidence of TB associated IRIS in HIV infected patients reported in various studies range from 15.2% to 41% 1, 2. The exact prevalence of non-HIV TB IRIS is not known. So far, only a few case reports have been published. Pediatric case reports in particular CNS – TB IRIS case reports are very scarce in number.

Case report:
An 8 year old female child presented with complains of high grade intermittent fever for one month duration and vomiting for 3 days. Clinical history and examination did not reveal any focus except for the history of contact with open case of tuberculosis in the neighborhood. On day 2 of admission the child developed altered sensorium and neck stiffness. CSF biochemical and microscopy was normal. CSF bacterial and fungal culture was negative. CT and MRI brain showed multiple tiny granulomas involving both the cerebral hemispheres and cerebellum. Fundus examination revealed bilateral pathognomic choroid tubercles. Retroviral study was negative. Based on the above findings and with a contact history of tuberculosis, the child was started on Category I ATT along with oral steroids. CSF culture (done by mycobacterium growth indicator tube) was positive for Mycobacterium tuberculosis. Clinical improvement was noted in the form of improved sensorium and appetite but fever was persistent. CSF culture and sensitivity reported (after 6 weeks of initiation of ATT) that the mycobacterium tuberculosis was resistant to all five first line anti-tubercular drugs. A diagnosis of MDR-TB was made and the child was started on 2nd line ATT and steroids were continued. There was clinical improvement; fever subsided by 2 weeks of initiation of 2nd line ATT and the child was discharged with advice to follow up. After 2 months of starting second line ATT, the child again presented with complains of high grade intermittent fever, vomiting for three days and altered sensorium for one day. Clinical examination did not show any focus and laboratory work up including CSF analysis did not reveal any infectious etiology. CT brain (plain and contrast) showed increase in size and number of tuberculomas compared to the multiple tiny granulomas (Images 1 & 2) being the initial diagnosis; which raised the suspicion of resistance to 2nd line ATT / poor drug compliance. History ruled out poor compliance. Repeat CSF was negative for AFB staining and CSF culture did not grow TB bacilli. In view of new onset symptoms and evidence of increasing size of tuberculomas, good compliance to treatment, a possibility of paradoxical response to TB treatment was considered after ruling out other infectious etiologies. Since IRIS is commonly known to occur in the setting of HIV, a repeat retroviral study was done which remained negative. The child was continued on second line ATT along with i.v. methylprednisolone. Clinical improvement was noted within 3 days of initiation of treatment with steroids in the form of improved sensorium and cessation of fever. The child recovered completely without any focal neurological deficit and was discharged after 10 days. Steroids were gradually tapered over 4 weeks and stopped. At present the child is doing well and is under regular follow up continuing the intensive phase of ATT.

Discussion:
Immune reconstitution inflammatory syndrome is defined as paradoxical response occurring during treatment as a result of restoration of immunity3. A wide number of terms used to describe this phenomenon are immune reconstitution inflammatory syndrome (IRIS), immune reconstitution syndrome (IRS), immune reconstitution disease (IRD), or paradoxical reactions /responses (PR) 4. Clinical symptoms include development of fever, newer lesions or increasing in size of existing lesions. It is a well-recognized phenomenon occurring in HIV patients started on ART while there is underlying unrecognized tuberculosis. Scenarios where IRIS can develop5 include (i) HIV negative patient on ATT, (ii) HIV positive patient not on ART but on ATT , (iii) Undiagnosed TB in HIV positive patients on ART.

IRIS has also been reported to occur in other immune compromised states like organ transplantation6. IRIS can also occur in the setting of non-TB infections like Mycobacterium avium complex infection, cryptococcal meningitis, CMV and herpes viruses.
Case definition:
There are no clear cut case definitions for non-HIV associated TB IRIS. Currently the available case definition given by the International Network for Study on HIV associated IRIS (INSHI) 3 for Paradoxical - TB IRIS is described in short:
A diagnosis of TB IRIS can be made in a patient diagnosed to have TB (pulmonary/extrapulmonary), who shows initial response to treatment and develops newer/enlarging TB lesions and/or constitutional symptoms within three months of institution of ART after excluding poor compliance, drug resistance, infections or neoplasm and drug toxicity.
The possible suggested mechanisms 5 for IRIS in non-HIV infected individuals are:
i. Hypersensitivity to antigens released during mycobacterial killing
ii. Exaggerated immune restoration following TB-induced immunosuppression occurring during TB treatment.
iii. Alteration in the response of the immune system due to change from the immunosuppressed anti-inflammatory to immune-competent pro-inflammatory state.

Treatment:
Being an inflammatory immune mediated response, IRIS responds to treatment with steroids and NSAIDS. Studies have demonstrated favourable outcome with both oral and intravenous steroids along with continuation of ATT6.

Conclusion:
* Non-HIV associated TB IRIS is rare but prevalent in our population.
* In any child with CNS TB while on ATT, development of tuberculomas does not always represent failure of drug treatment, paradoxical response should be considered. Appropriate timely initiation of treatment improves the outcome.
* IRIS remains as a poorly understood entity. Further research is required to study the underlying pathogenesis in these patients.

References: