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TEACHING FILES (GRAND ROUNDS)

INH MONORESISTANCE TUBERCULOSIS WITH INHA GENE RESISTANCE - WHAT SHOULD BE THE ANTI-TUBERCULOSIS REGIMEN?

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Clinical Problem:
A 4-year-old boy presented with gradually increasing left axillary swelling for 7 months. There is no fever, cough, loss of appetite or weight loss or contact with a patient having tuberculosis (TB) contact. He had received immunization as per Universal Immunization programme (UIP) schedule including BCG at birth. On examination, weight was 15.5 kg (between 3rd-50th centile as per World Health Organisation (WHO) growth charts) and height was 97 cm (between 3rd-50th centile as per WHO growth charts). There was a left axillary non-tender, matted and mobile swelling. Systemic examination was normal. Hemogram showed haemoglobin of 9.5 gm/dL, total leucocyte count of 13690/cumm (61% neutrophils and 30% of lymphocytes) and platelets 644 x 10^3/ul. Erythrocyte sedimentation rate (ESR) was 134 mm/hr. Chest Xray showed right upper and middle zone consolidation. Ultrasound (USG) of the swelling and abdomen showed small hypoechoic node in bilateral axilla, measuring 8 x 6 mm and 9 x 3 mm, central echogenic hilum maintained. HRCT chest showed subsegmental consolidation in anterior segment of right upper lobe with air bronchogram, multifoci of intraparenchymal coarse calcification within consolidation. Ill defined-multiple conglomerated mediastinal lymph node present. Right hilar lymphadenopathy was seen causing narrowing of middle lobe bronchus and multiple enlarged lymph node in left axilla. An excision of the axillary node was done that showed mycobacterium tuberculosis (MTB) with no rifampicin resistance on Xpert MTB/Rif assay. Histopathology of the node showed chronic granulomatous lymphadenitis extending upto subcutaneous tissue compatible with TB. Child was started on first line anti-tubercular therapy (ATT) comprising of Isoniazid (INH), Rifampicin (RIF), Pyrazinamide and Ethambutol. On follow up with Line Probe Assay (LPA) report showed resistance to inhA gene and sensitive to rpob and KatG gene and 6 week MGIT showed growth of MTB. Child was diagnosed as disseminated tuberculosis with INH monoresistance with inhA gene resistance and KatG gene susceptible.

What treatment regimen should be given in a child with disseminated TB with INH mono-resistant with inhA gene resistance and KatG gene sensitive?

Discussion:
INH is a crucial first-line drug for treating TB due to its strong ability to kill the bacteria in the early stages of infection.[1] Unfortunately, resistance to INH has become the most widespread form of resistance to anti-TB drugs, whether on its own or in combination with other medications.[1] According to global statistics (2018), INH resistance without concurrent RIF resistance was observed in 7.1% of new TB cases and 7.9% of previously treated TB cases.[2] INH mono-resistance refers to the resistance of TB bacteria to only one of the first-line drugs, specifically INH, while remaining susceptible to other anti-TB drugs.[3] The most common causes of INH resistance are mutations in genes such as katG or inhA and less common in other genes such as ahpC32 gene.[4,5] INH is converted into an active form by an enzyme called catalase-peroxidase, which is regulated by the katG gene.[1] Mutations in katG, particularly at the Ser315Thr location, lead to a high level of INH resistance.(6,7) The inhA gene encodes an enzyme that plays a role in fatty acid synthesis in TB bacteria, which is the target of the active derivative of INH.[1] Mutations in inhA or its promoter region prevent INH from binding, resulting in low-level resistance to the drug.[8] Resistance to ethionamide and prothionamide is also typically seen in isolates with inhA mutations.[9] WHO recommendation in INH resistant TB is treatment with rifampicin, pyrazinamide, ethambutol and levofloxacin for duration of 6 months.[3] The use of high dose isoniazid (10-15 mg/kg/day) is not reviewed due to insufficient data however Guideline Development Group discussed the effect of increased dosing depending on the type of molecular mutations seen.[3] In vitro studies suggest that in inhA mutations and in absence of KatG mutations high dose isoniazid could be effective and can be

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considered as part of treatment.[3] National Tuberculosis Elimination Programme (NTEP) recommendation is similar to the WHO guidelines. The regimen addition of levofloxacin vs the use of high dose isoniazid needs to be further evaluated but looking at the scientific approach high dose isoniazid would be effective and should be considered in such a patient. In our patient, we continued a regime without INH as per the NTEP recommendations.

Compliance with ethical standards

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Conflict of Interest: None

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