A single-centre experience on *Mycobacterium tuberculosis complex* infection in children with primary immunodeficiency

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Introduction

Universal vaccination with Calmette-Guérin bacillus (BCG), recommended[1] and widespread in countries with a high incidence of tuberculosis[2] is contraindicated in the suspicion of congenital or acquired immunodeficiency[1]. About 50% of patients with severe combined immunodeficiency (SCID) exposed to BCG develops disease, often in disseminated form[3]. Mortality, historically of 80%[4], it accounts for 25% of symptomatic cases[3].

Aim

To describe *Mycobacterium tuberculosis complex* (MTBC) infections in children with primary immuno-deficiencies (PIDs).

Methods

Single-centre retrospective study on children with PIDs [adenosine deaminase deficiency (ADA-SCID), Wiskott-Aldrich syndrome (WAS)] referred from 2002 to 2020.

We analyse incidence, anti-tuberculosis treatment and outcome of MTBC infections [latent tuberculosis infection (LTBI), tuberculosis (TB), disease after BCG vaccine (BCG-itis)].

Results

Among fifty ADA-SCID children, 21% (10/47, 3 missing data) received BCG and 8% (4/50) experienced MTBC infection.

Two patients developed disseminated BCG-itis, while two others experienced localized BCG-itis (Table 1).

The remaining six children subjected to BCG did not develop disease: 2/6 received anti-TB prophylaxis at ADA-SCID diagnoses, while 4/6 did not (2/4 late onset ADA-SCID, 1/4 died because of lymphoma).

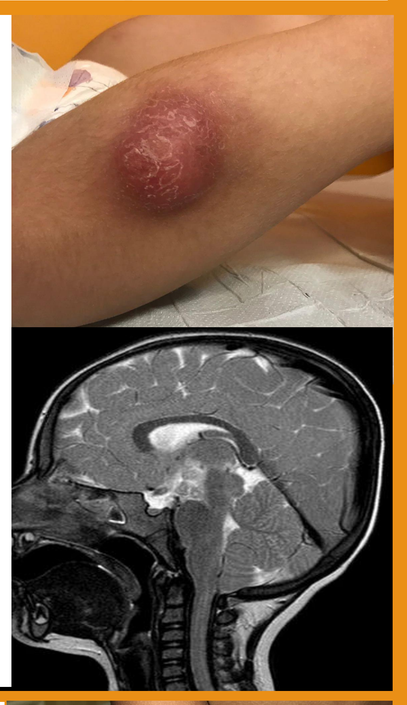
Table 1. Characteristics of ADA-SCID children who developed BCG-itis.

#	BCG	Ly count*	Country	BCG-itis (Diagnose/Site)	Therapy (Drugs/Duration)§
1	At birth	Ly 140/uL	Saudi Arabia	4 months/**Disseminated** (lymph-nodes, skin, lungs)	I-R-E-A/14 months
2	6 months	T-cells 39/uL	Turkey	29 months/**Disseminated** (skin abscesses, central nervous system)	I-R-E-M/12 months
3	At birth	Ly 100/uL	Saudi Arabia	9 months/**Localized** (inoculum site)	R-E-O/6 months
4	20 days	Ly <250/uL	Brazil	7 months/**Localized** (lymph-node)	I-R-E/18 months

Legend: I, isoniazid; R, rifampin; E, ethambutol; O, ofloxacin; A, amikacin; M, moxifloxacin * Lymphocytes count (or T-cells count whenever available) at the diagnose of ADA-SCID § **We acknowledge that anti-mycobacterial therapies have been unconventional, mostly performed more than 10 years ago in the country of children's origin**

Patients #1, #3 and #4 underwent successful hematopoietic stem and progenitor cell gene-therapy (GT), achieving immune reconstitution and systemic detoxification.

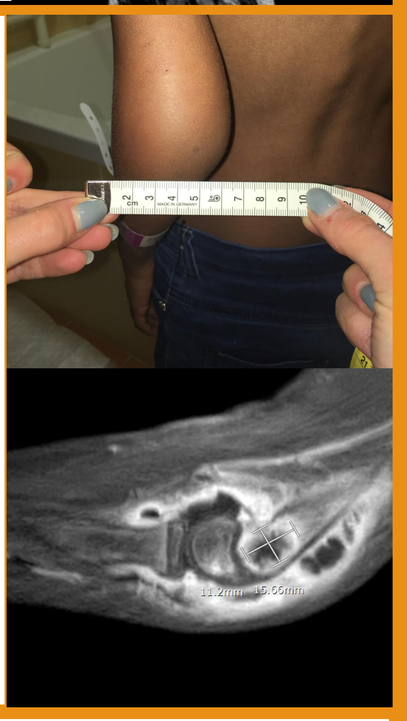
Unfortunately, GT in patient #2 (Figure 1) was not successful. She continued I-R for 12 more months, eventually undergoing haploidentical alfa-beta depleted stem cell transplantation (SCT). The procedure was complicated by refractory hemophagocytic lymphohistiocitis-related graft failure that required treatment with emapalumab, without BCG disease reactivation, and an additional SCT. She is alive18-months after SCT, with good immune reconstitution, without active infection 11-months after anti-TB therapy suspension.



Among twenty-three WAS children, 50% (10/20, 3 missing data) received BCG and 8.7% (2/23) experienced MTBC infection.

One patient developed localized BCG-itis [vaccination at 45-days of age, 3-months I-levofloxacin (L)].

Another one (vaccination at 1-month of age) was diagnosed with LTBI when he was 9 years-old (3 months I-R). Two months later, he developed TB (Figure 2, unilateral elbow arthritis with osteomyelitis due to I-resistant *Mycobacterium tuberculosis* Dehli-CAS) treated with R-E-L-pyrazinamide for 9 months; he underwent GT, completing additional 9 months of R-E-high dose I.



Conclusions

MTBC infections deserve high clinical suspicion in children with PIDs. A timely diagnosis and anti-TB treatment are fundamental to contain mortality and allow a curative therapy of underlying disease.

References

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