Enfermedades Infecciosas y Microbiología Clínica 40 (2022) 423–427

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Original article

Tuberculosis screening after detection of a case in a paediatric haemato-oncology unit in a low prevalence country

Carlos Daniel Grasa Lozano[a,b,c,*], María Baro-Fernández[d], Alba Rubio-San-Simón[d], Daniel Blázquez-Gamero[a,b], Paula López-Roa[e], Constanza Liébana[f], Pilar Guerra-García[d], Cinta Moraleda[a,b], Cristina Epalza[a,b]

[a] *Paediatric Infectious Diseases Unit, Department of Paediatrics, Hospital Universitario 12 de Octubre, Universidad Complutense de Madrid, Spain*
[b] *Instituto de Investigación Hospital 12 de Octubre (imas12), Spain*
[c] *Paediatric Infectious Diseases Unit, Department of Paediatrics, Hospital Universitario La Paz, Madrid, Spain*
[d] *Paediatric Haemato-Oncology Unit, Department of Paediatrics, Hospital Universitario 12 de Octubre, Universidad Complutense de Madrid, Spain*
[e] *Microbiology Department, Hospital Universitario 12 de Octubre, Universidad Complutense de Madrid, Spain*
[f] *Paediatric Radiology Unit, Hospital Universitario 12 de Octubre, Universidad Complutense de Madrid, Spain*

ARTICLE INFO

Article history:
Received 15 September 2020
Accepted 17 December 2020
Available online 21 February 2021

Keywords:
Tuberculosis
Haemato-oncology
Paediatrics
Screening

ABSTRACT

Background: There are no guidelines to screen haemato-oncologic children when a tuberculosis (TB) outbreak is suspected.
Methods: After exposition to an adult with active TB, children exposed from a haemato-oncology unit were screened according to immunosuppression status and time of exposure. Until an evaluation after 8–12 weeks from last exposure, isoniazid was indicated to those with negative initial work-up.
Results: After 210 interventions, we detected a case of pulmonary TB, and another with latent TB infection. Pulmonary findings and treatment approach were challenging in some patients.
Conclusions: The TB screening of oncologic children required a multidisciplinary approach, and clinicians managed challenging situations.

Cribado de tuberculosis tras la detección de un caso en una unidad de hematooncología pediátrica en un país con baja prevalencia

Palabras clave:
Tuberculosis
Hematooncología
Pacientes pediátricos
Cribado

RESUMEN

Antecedentes: No existen pautas para el cribado de niños hematooncológicos cuando se sospecha de un brote de tuberculosis (TB).
Métodos: Después de la exposición a un adulto con TB activa, se evaluó a los niños expuestos de una unidad de hematooncología según el estado de inmunosupresión y el tiempo de exposición. Hasta una evaluación después de ocho a12 semanas desde la última exposición, se indicó isoniazida para aquellos con un proceso inicial negativo.
Resultados: Tras 210 intervenciones se detectó un caso de tuberculosis pulmonar y otro con infección por TB latente. Los hallazgos pulmonares y el método de tratamiento fueron un desafío en algunos pacientes.
Conclusiones: El cribado de TB en niños oncológicos requirió un método multidisciplinario y los médicos manejaron situaciones complejas.

Abbreviations: HR, high risk; IGRA, interferon-gamma release assays; LTBI, latent tuberculosis infection; TB, tuberculosis; TST, tuberculin skin test; QFT-GIT, QuantiFERON® TB Gold In-Tube.

* Corresponding author.
E-mail address: carlosgrasa@gmail.com (C.D. Grasa Lozano).

https://doi.org/10.1016/j.eimc.2020.12.017

Introduction

According to the nature of tuberculosis (TB), the risk of transmission can be stratified depending on the exposition, contagiousness of index case and contact susceptibility.[1] Regarding susceptibility, immunocompromised patients and children have an increased risk of developing severe disease.

Although existing guidelines are useful to design a strategy when a TB case is diagnosed, there is no specific approach for exposed children with haemato-oncological conditions.[1,2]

The aim of this report is to describe our experience when the mother of a patient admitted to a paediatric haemato-oncology unit was diagnosed with active pulmonary TB and the medical actions derived from this situation.

Material and methods

A 28-year-old woman from Honduras was diagnosed with smear-positive pulmonary TB while her daughter was an inpatient receiving chemotherapy for a low-grade glioma. She had previously accompanied her daughter to all medical visits. Therefore, once diagnosed, all the clinic days, daycare visits and admissions of her daughter, for the previous 3 months, were tracked.[1] All potential exposed patients were detected.

Following guidelines[1] adapted to inhospital exposure, patients were stratified into different "exposure circles": circle 1, if the patient had shared more than 8 h of cumulative exposure in the same enclosed space (ward or outpatient clinic) and circle 2, if the child had shared less than 8 h or had been admitted simultaneously but in a different room. In case it was not possible to precise the time of exposure for each patient in the same enclosed space with the index case, that patient was considered from circle 1. A high-risk (HR) group included those patients receiving active immunosuppressive therapy during exposure. Children included in circle 1 and/or HR group were immediately studied; those from circle 2, and not included in the HR group, were screened once evaluation of circle 1 was completed.

All patients underwent a medical interview, physical examination, tuberculin skin test (TST), interferon-gamma release assay (IGRA) (QuantiFERON® TB Gold In-Tube-QFT-GIT-, Cellestis, Ltd.) and chest X-ray. Tests were repeated 8–12 weeks after last exposure, when first evaluation had been performed before 8 weeks. A cut-off value of 5 mm was considered positive for TST in this cohort.

The study of potential exposition/infection of healthcare workers and patients' relatives was delegated on the Department of Occupational Medicine and Public Health. Results are not included in this study.

Results

Thirty-two patients were considered for screening. Synopsis of demographics and results of diagnostic tests are included in Table 1. All cases were HIV negative. The screening flowchart is shown in Fig. 1.

The daughter of the index case presented a positive TST (15 mm), an indeterminate IGRA result, an infiltrate in the chest X-ray and she was diagnosed with pulmonary TB; no TST was performed before chemotherapy started. Her chemotherapy was withheld while she received treatment against TB.

After second evaluation, a patient with an intermediate risk B-cell acute lymphoblastic leukaemia turned a previous negative TST to positive. IGRA tests were negative and chest X-rays were normal, so he was diagnosed of latent tuberculosis infection (LTBI) and received isoniazid for 6 months; study of householders was negative for TB. He continued chemotherapy as scheduled. He was part of circle 1 and from the HR group.

In 2 cases chest X-ray evaluations were challenging: 1 patient with Hodgkin lymphoma presented a pulmonary nodule (a later biopsy revealed progression of his underlying disease), and another patient's chest X-ray evaluation was performed during an episode of fever and neutropenia and showed an infiltrate, with a complete resolution after the febrile episode.

Screening with TST before immunosuppressive treatment had been performed in 16/28 (57%) (14/26 – 54% – of those with haemato-oncological diagnosis) and none of them had screening with IGRA. No adverse events were reported related to TB medication. Finally, 210 hospital activities were necessary, including 84 interviews throughout 4 months.

Discussion

Diagnosing TB in a patient with immunosuppression is challenging, especially in paediatric population.[1,3–6] Stefan et al. described discordant results when using 3 different tests (TST and two IGRA methods: T-SPOT.TB and QFT-GIT) to rule out TB in a group of 34 oncological children. They prompted to combine different tests to confirm or rule out infection, due to discrepancies between cases.[6] Carvalho et al. stated that T-SPOT is more accurate to identify TB infection when compared to QFT-GIT in children with lymphocytopenia, after testing 18 patients with this condition.[4] In our case, T-SPOT was not available, so we decided to use TST, QFT-GIT and chest X-ray, given the aforementioned difficulties in this population.

Erkens et al. suggested to stratify contacts in circles given the time shared in the same enclosed space with a source case and encouraged to evaluate these contacts prioritizing by personal conditions, as an increased risk for developing TB after infection.[1] This is the rationale we used to stratify patients and prioritize their screening. It was impossible to ascertain the time of exposure, so we considered one day of shared visit (if admitted or sharing waiting room/treatment room in daycare) as spending at least 8 h sharing an enclosed space and we investigated them as in the Italian cohort.[4] We differentiated urgent screening or to be done as soon as possible, according to individual risk. This implied a considerable use of resources in a short period of time, so planning rationally from the beginning was crucial.

The importance of ruling out TB infection after exposure to an index case in this population is out of discussion, not only because of the patient's personal benefit but also because of the potential risk of dissemination.[1,3,4,6,7] In our cohort, we detected a case of LTBI and there are other cases of TB infection after inhospital exposure reported, not only in patients but also in relatives and workers.[4,7]

Timely diagnosis and treatment of TB infection could avoid challenging situations due to interactions of TB drugs, as well as treating LTBI with shorter and simpler schemes than in pulmonary TB. Hepatotoxicity of isoniazid, rifampin and pyrazinamide is well known and these drugs can interact with many others, delaying chemotherapy. Two patients did not receive prophylactic therapy with isoniazid due to elevation of liver enzymes, caused by underlying oncological condition, but symptoms were carefully monitored until second evaluation 8-weeks after last exposure was done, which concluded no TB infection.

Diagnosis is not only challenging due to test discrepancies and potential false negatives results, but also due to a possible pulmonary involvement of the underlying disease or other respiratory infections that can mimic TB. Therefore, we should bear in mind these possibilities as occurred in two of our patients; similar cases have been reported.[3,6,8,9]

Table 1
Socio-demographic, clinical and tuberculosis screening data of patients.

Patient	Age (years)	Baseline diagnosis	First TST (mm)	First QFT	First chest X-ray	Time until evaluation (1st/2nd)**	Second TST (mm)	Second QFT	Second chest X-ray	Final diagnosis	Comments
1	12	Low grade glioma	15	I	Infiltrate in lung	1/NP	NP	NP	NP	Pulmonary TB	Daughter of index case
2*	7	B-cell ALL	0	N	Normal	5/11	6	N	Normal	TB contact – LITB	H until 2nd, then Tx
3*	2	B-cell ALL	0	I	Normal	5/10	0	N	Normal	TB contact	No prophylaxis due to hepatitis
4*	11	HLH	0	N	Normal	4/9	0	N	Normal	TB contact	No prophylaxis due to hepatitis
5*	13	Classic HL	0	N	Normal	2/10	0	N	Normal	TB contact	H until 2nd
6*	2	B-cell ALL	0	N	Normal	4/12	0	N	Normal	TB contact	H until 2nd
7*	3	Medulloblastoma	0	N	Normal	3/11	0	N	Normal	TB contact	H until 2nd
8*	3	CMMRD, T-cell ALL	0	N	Normal	4/11	0	N	Normal	TB contact	H until 2nd
9*	3	B-cell ALL	0	N	Normal	3/11	0	N	Normal	TB contact	H until 2nd
10	4	LCH	0	N	Normal	6/14	0	N	Abnormal → Normal	TB contact	H until 2nd Infiltrate resolved with antibiotics
11	6	Burkitt lymphoma	0	N	Normal	7/11	0	N	Normal	TB contact	H until 2nd
12	3	B-cell ALL	0	N	Normal	5/11	0	N	Normal	TB contact	H until 2nd
13	13	Thyroid Ca	0	N	Normal	3/9	0	N	Normal	TB contact	H until 2nd
14	4	Pilocytic astrocitoma	0	N	Normal	10/NP	NP	NP	NP	TB contact	–
15	5	B-cell ALL	0	N	Normal	11/NP	NP	NP	NP	TB contact	–
16	5	Burkitt lymphoma	0	N	Normal	14/NP	NP	NP	NP	TB contact	–
17	2	Neuroblastoma	0	N	Normal	7/11	0	N	Normal	TB contact	H until 2nd
18	2	Pro-B LLA	0	N	Normal	7/13	0	N	Normal	TB contact	H until 2nd
19	14	Classic HL	0	N	Nodule	8/NP	NP	NP	NP	TB contact	Nodule due to oncological process
20	1	Cerebellar tumour	0	N	Normal	12/NP	NP	NP	NP	TB contact	–
21*	4	Pre-B B-cell LLA	0	N	Normal	5/12	NP	N	Normal	TB contact	Transferred to other hospital
22*	7	B-cell ALL	NP	N	Normal	2/15	NP	N	Normal	TB contact	Transferred to other hospital
23*	6	B-cell ALL	NP	N	Normal	7/14	NP	N	Normal	TB contact	Transferred to other hospital
24*	7	Ependymoma	NP	NP	NP	NP/NP	NP	NP	NP	TB contact	Palliative care
25*	14	B-cell ALL	0	N	Normal	3/11	NP	N	Normal	TB contact	No Px due to minimum risk for isolation
26*	13	CIDP	0	N	Normal	9/NP	NP	NP	NP	TB contact	–
27*	9	Nephrotic Sd.	0	N	Normal	12/NP	NP	NP	NP	TB contact	–
28	2	SCD	0	N	Normal	10/NP	NP	NP	NP	TB contact	–
29	12	SCD	0	N	Normal	12/NP	NP	NP	NP	TB contact	–
30	12	Burkitt ALL	0	N	Normal	12/NP	NP	NP	NP	TB contact	–
31	3	ITP	0	N	Normal	11/NP	NP	NP	NP	TB contact	–
32	11	SCD	8	N	Normal	14/NP	NP	NP	NP	TB contact	BCG vaccine, negative QFT

Above slashed line, are patients who belonged to circle 1 (>8 h with index case).
I, indeterminate; N, negative; NP, not performed; H, isoniazid; ALL, acute lymphoblastic leukaemia; HLH, hemophagocytic lymphohistiocytosis; HL, Hodgkin lymphoma; LCH, Langerhans cell histiocytosis; CIDP, chronic inflammatory demyelinating polyneuropathy; ITP, idiopathic thrombocytopenic purpura; SCD: sickle cell disease; LITB, latent tuberculosis infection; Tx, treatment; Px: prophylaxis.

* High-risk patients due to immunosuppression.

** Time (weeks) from last exposure until 1st and 2nd evaluation.

Moreover, TB should be ruled out before starting chemotherapy due to the risk of progression of a latent TB infection when immunosuppression is started.[3,8,10] Stefan et al. reported 17.6% of diagnosis of TB in a cohort of 34 children screened before chemotherapy in South Africa, a country with a high TB incidence.[6,11] On our cohort, only 14 children (54%) had TST prior to starting chemotherapy. Some of them were referred from other hospitals or received urgent chemotherapy treatment, but in other cases there were no reasons for this lack of testing. Even in a low TB incidence country like Spain TB is convenient to be ruled out before immunosuppressive therapy.

It is advisable that as soon it is known that a patient requires immunosuppressive therapy, TB screening is performed. Whether it is not possible to wait for screening results, at least it would be convenient to perform TST and/or IGRA before starting immunosuppression. Despite the convenience of TB screening for all these patients, it is especially important for those coming from medium-high burden TB countries and if there has been a potential contact to a TB case. Adaptation of local guidelines to screen TB before starting chemotherapy could benefit haemato-oncological patients preventing progression from latent to active TB.

Management of TB contacts in a paediatric haemato-oncology unit is challenging. Underlying diseases might mimic TB and diagnostic tests can show discrepancies and lower performance than in healthy patients.

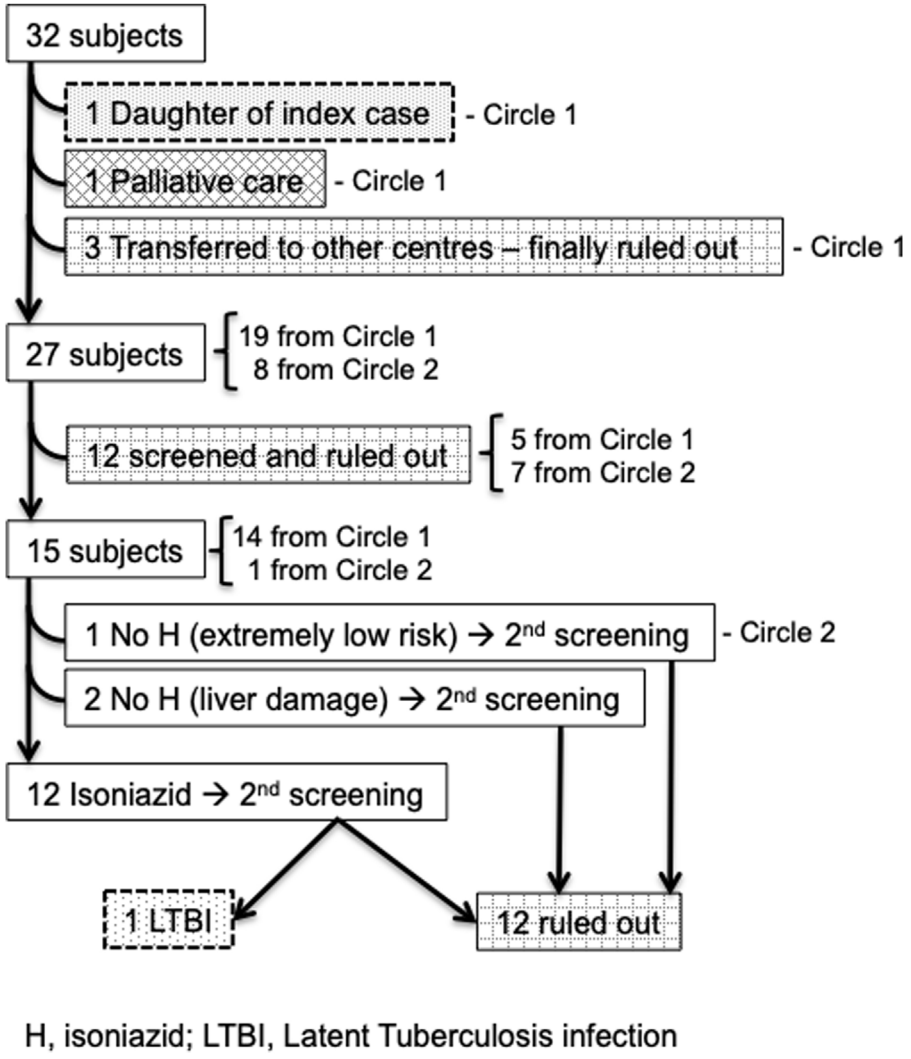

Fig. 1. Flow of screening and diagnosis. H, isoniazid; LTBI, latent tuberculosis infection.

The approach to oncologic children exposed to TB involved a multidisciplinary team and a considerable use of resources in a short period of time.

Ethics

Research ethics committee from Hospital 12 de Octubre approved this work, in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by CDG, CE, MBF, ARSS, DBG, CL, PLR, PGG and CM. The first draft of the manuscript was written by Carlos Daniel Grasa Lozano and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

CDG is funded by the Spanish Ministry of Science and Innovation—Instituto de Salud Carlos III and Fondos FEDER (Contrato Río Hortega CM19/00015).

Conflicts of interest

None of the authors have conflict of interest, financial or otherwise related to this manuscript.

Acknowledgements

We would like to acknowledge all the workers from paediatric haemato-oncology, paediatric infectious diseases, paediatric radiology and microbiology departments.

References

1. Erkens CGM, Kamphorst M, Abubakar I, Bothamley GH, Chemtob D, Haas W, et al. Tuberculosis contact investigation in low prevalence countries: a European consensus. Eur Respir J [Internet]. 2010;36:925–49. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20889463 [cited 12.04.18].
2. Ustero PA, Kay AW, Ngo K, Golin R, Tsabedze B, Mzileni B, et al. School and household tuberculosis contact investigations in Swaziland: active TB case finding in a high HIV/TB burden setting. PLoS ONE [Internet]. 2017;12:e0178873. Available from: https://dx.plos.org/10.1371/journal.pone.0178873 [cited 04.07.19].
3. Cruz AT, Airewele G, Starke JR. Tuberculosis in pediatric oncology and bone marrow transplantation patients. Pediatr Blood Cancer [Internet]. 2014;61:1484–5. Available from: http://doi.wiley.com/10.1002/pbc.24985 [cited 11.08.19].
4. Carvalho ACC, Schumacher RF, Bigoni S, Soncini E, Notarangelo L, Apostoli A, et al. Contact investigation based on serial interferon-gamma release assays (IGRA) in children from the hematology-oncology ward after exposure to a patient with

pulmonary tuberculosis. Infection [Internet]. 2013;41:827–31. Available from: http://link.springer.com/10.1007/s15010-013-0450-y [cited 04.07.19].
5. Bruzzese E, Bocchino M, Assante LR, Alessio M, Bellofiore B, Bruzzese D, et al. Gamma interferon release assays for diagnosis of tuberculosis infection in immune-compromised children in a country in which the prevalence of tuberculosis is low. J Clin Microbiol [Internet]. 2009;47:2355–7. Available from: http://jcm.asm.org/cgi/doi/10.1128/JCM.01320-08 [cited 04.07.19].
6. Stefan DC, Dippenaar A, Detjen AK, Schaaf HS, Marais BJ, Kriel B, et al. Interferon-gamma release assays for the detection of Mycobacterium tuberculosis infection in children with cancer. Int J Tuberculosis Lung Dis [Internet]. 2010;14:689–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20487605 [cited 04.07.19].
7. Lee EH, Graham PL, O'Keefe M, Fuentes L, Saiman L. Nosocomial transmission of Mycobacterium tuberculosis in a children's hospital. Int J Tuberculosis Lung Dis [Internet]. 2005;9:689–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15971399 [cited 04.07.19].
8. Karakas Z, Agaoglu L, Taravari B, Saribeyoglu E, Somer A, Guler N, et al. Pulmonary tuberculosis in children with Hodgkin's lymphoma. Hematol J [Internet]. 2003;4:78–81. Available from: http://www.nature.com/doifinder/10.1038/sj.thj.6200219 [cited 11.08.19].
9. Chandar R, Gopakumar KG, Appanraj P, Thankamony P. Pulmonary cavitation, odontoid lytic lesion, and B symptoms: early suspicion of the fine line between Hodgkin lymphoma and tuberculosis. Pediatr Blood Cancer [Internet]. 2018;65:e27355. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30039910 [cited 08.04.20].
10. Starke JR. Interferon-γ release assays for diagnosis of tuberculosis infection and disease in children. Pediatrics [Internet]. 2014;134. Available from: https://pubmed.ncbi.nlm.nih.gov/25422024/ [cited 08.12.20].
11. World Health Organization. WHO Global Tuberculosis Report 2018 [Internet]. Pharmacological Reports, vol. 69. World Health Organization; 2018. Available from: https://www.who.int/tb/publications/global_report/en/ [cited 14.08.19].