

MESA: Brotes de TB

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Brote de tuberculosis: la importancia de los bares en los estudios de contactos

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Introducción

La prevalencia de la infección entre los contactos de enfermos de tuberculosis (TB) se sitúa alrededor del 30%¹, muy superior a la de la población general. Este riesgo varía según variables de las personas expuestas, del caso índice y de las características de la exposición¹. El miedo asociado al estigma que ocasiona la enfermedad puede constituir una barrera importante para conseguir un estudio exhaustivo y completo de los contactos². Los bares son lugares de encuentro y socialización en los que puede ser difícil realizar estudios de contactos en casos de TB³.

El objetivo del trabajo fue describir un brote tuberculosis ocurrido en bares e investigado según la técnica de los círculos concéntricos, en el que la falta de colaboración del caso índice comportó retraso y dificultad en la realización del estudio.

Métodos

La Unidad de Vigilancia Epidemiológica de Lleida, el día 19 de marzo de 2012, recibió la notificación de un caso de tuberculosis pulmonar de un varón de 42 años con cuadro clínico de tos, pérdida de peso y que presentaba además lesiones bilaterales en el parénquima pulmonar con múltiples imágenes pseudonodulares diseminadas con cavidades. La baciloscopia y el cultivo de esputo eran positivos.

El paciente localizó a dos contactos familiares para estudiar, pero se negó sistemáticamente a identificar a otros contactos en el ámbito de la empresa o en espacios lúdicos. Después de dos meses de intentos infructuosos para conseguir su colaboración, se contactó con los responsables de salud laboral de la empresa

donde trabajaba. Mediante la inspección ocular del centro de trabajo y del bar de la empresa se elaboró un censo de contactos a estudiar y en función del nivel de exposición se establecieron cinco círculos de exposición. También se estudiaron otros ámbitos lúdicos (tres bares del barrio de residencia del caso índice), los familiares de todos los casos y una segunda empresa relacionada con un caso secundario.

A todos los contactos se les ofreció la PT (PPD RT 23 conTwen 80, 2 UT por 0,1 ml). La prueba se consideró positiva en induración igual o superior a 5 mm. A todos los positivos a la PT se les propuso radiografía de tórax, visita médica e indicación del tratamiento de la infección tuberculosa latente (ITL) o de la enfermedad según estuviera indicado.

La principal medida de frecuencia fue la prevalencia de la ITL y su asociación con el círculo de exposición se determinó con la odds ratio (OR) y su intervalo de confianza del 95% (IC 95%). El análisis de los datos se realizó con el programa estadístico Epiinfo v.7.

Resultados

Iniciaron el estudio 404 de los 414 contactos censados (97,6%). La edad media era de 38,1 años ($\pm 11,7$) y el 29,0% eran mujeres. Los contactos estaban distribuidos según los siguientes ámbitos de exposición: 316 en la empresa del caso índice, 58 en los tres bares del barrio, 18 familiares de los casos y 12 en la empresa de un caso secundario.

El caso índice se detectó en el mes de marzo de 2012. En los siete meses siguientes se detectaron nueve casos más. Este

Tabla 1. Riesgo de infección tuberculosa en el bar de la empresa del caso índice

Círculo de contacto	Prevalencia	OR	CI 95%
Primero	96,0 (24/25)	27,6	3,4-222,7
Segundo	73,6 (39/53)	3,2	1,4-7,5
Tercero	58,9 (33/56)	1,7	0,7-3,7
Cuarto	48,2 (67/139)	1,1	0,5-2,1
Quinto	46,5 (20/43)	1,0	
Total	57,9 (183/316)		

χ^2 de tendencia lineal = 25,1; $p > 0,0001$ (círculo de contacto)
OR^a, odds ratio; IC^b, intervalo de confianza

primer caso (caso índice) presentó un retraso diagnóstico de más de 6 meses, lesiones cavernosas y baciloscopia del esputo positiva y se negó a colaborar para identificar contactos de riesgo. El segundo caso fue uno de los clientes de los bares del barrio que frecuentaba el primer caso y que presentó una tuberculosis pleural. Este paciente permitió identificar los tres bares del barrio que frecuentaba este primer caso. En la misma empresa del caso índice aparecieron 5 casos (prevalencia 1,6%; 5/316). Cuatro casos se detectaron durante el estudio de contactos en la empresa y otro con posterioridad. Dos hijos de 2 y 6 años de este quinto caso también enfermaron (prevalencia entre los familiares del 11%; 2/18). En el estudio entre los clientes de los bares del barrio apareció un segundo caso (2,3%; 2/58).

Las prevalencias de la ITL en los diferentes ámbitos de exposición fueron muy elevadas: 57,9% (183/316) en la empresa del caso índice, 51,7% (30/58) en los tres bares del barrio, 38,9% (7/18) entre los familiares de casos y 33,3% (4/12) en la empresa de un caso secundario. En el bar de la empresa se observó una relación dosis respuesta (Tabla 1).

Discusión

Mediante la técnica de los círculos concéntricos se realizó un estudio de contactos en 404 personas expuestas entre los que se detectaron 9 casos de tuberculosis, se observó una alta pre-

valencia de la ITL (55,4%) y la existencia de dosis-respuesta entre los expuestos al bar de la empresa del caso índice. El estudio se pudo realizar a pesar de la falta de colaboración del caso índice.

Las estrategias para reducir el estigma y mejorar los sistemas de entrevista con los pacientes deberían ser objeto de investigación para evitar retrasos y mejorar la exhaustividad del estudio de contactos². Los bares pueden ser lugares de transmisión y dada la frecuentación de estos establecimientos deben ser considerados posibles ámbitos de exposición en el caso de tuberculosis cavitarias entre sus trabajadores o clientes³⁻⁵.

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Emergence of tuberculosis disease by *Mycobacterium bovis*-BCG in cancer patients without intravesical BCG Instillation

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Introduction

BCG, an attenuated strain of *Mycobacterium bovis*, is widely used as adjunctive therapy for superficial bladder cancer¹. The intravesical administration of BCG has been related with systemic infectious complications². Outside this scenario, the occurrence of tuberculosis (TB) caused by BCG is extremely rare³.

In September 2013, a patient was diagnosed with pulmonary TB disease due to BCG at the Hospital de Barcelona, Barcelona, Spain. The specific route of acquisition of the infection remained unclear. In 2015, two other patients at the same hospital were diagnosed with systemic TB disease caused by BCG. As a result, the clinical features and risk factors of these three patients were examined. None of them had received either intravesical BCG or BCG vaccination; they had all previously received chemotherapy for a non-bladder cancer and they all had a CVC with an implantable port (Port-a-Cath®). The maintenance and heparinization of their CVC was performed in an outpatient setting where other patients received intravesical BCG instillations. We contacted the Public Health Agency of Barcelona to study this cluster of cases and to determine the mechanism of BCG infection, and thus to identify or prevent other possible cases. We report nine cases of nosocomial TB disease in patients who had not received previous intravesical BCG instillation.

Epidemiological study

All strains of *M. bovis*-BCG isolated from January 1, 2012 to December 31, 2015 at the microbiology laboratories of the four largest hospitals in Barcelona were collected. The registers of the TB programs of Barcelona and Catalonia from January 1, 2005 to December 31, 2015 were also consulted searching for TB caused by *M. bovis* or *M. bovis*-BCG. Patients with TB-BCG disease who had not received intravesical BCG instillation were included in the study. "Risk patient visits" were considered visits in which the CVC maintenance was performed within 15 days of an intravesical BCG instillation in the same room at a given

center. Incubation times were estimated from each risk visit to the onset of symptoms.

From 2005 to 2015, 50 people were diagnosed with TB caused by *M. bovis* or *M. bovis*-BCG (TB-BCG) and nine met the study's inclusion criteria. At the time of diagnosis of TB-BCG, all patients had long-term CVC, which was periodically maintained at four different outpatient oncology clinics. These facilities were oncological offices at which other patients received intravesical BCG Onco-TICE® instillations for bladder cancer. Several deviations from appropriate operating procedures in BCG management were observed in these four-oncology clinics⁴.

Complete data of all patient visits for BCG instillation and for the maintenance of CVC from January 1, 2014 to December 31, 2015 were recorded at one clinic. Two out of nine patients (22.2%) who performed CVC maintenance developed TB-BCG. These nine patients accumulated 37 visits for maintenance of their CVC. Fourteen out of 37 visits met the criteria of risk visit. The incidence of TB-BCG among the risk expositions was: 2 out of 14: 14,2 %.

The six patients diagnosed with TB-BCG between 2012 and 2015 accumulated a total of 43 maintenance visits. Twelve of these visits met the criteria for risk visit. The possible incubation periods ranged from 47 to 319 days, with a median of 166 days. In the three patients with only one risk exposure, possible incubation periods were 381, 47 and 57 days respectively.

Clinical and microbiological study

The median age of patients was 69 years (range 47–80 years) and five (56%) were female. All had a history of solid cancer and had a permanent CVC. At the onset of TB all patients had no evidence of cancer disease, or their cancer was stable. None were receiving chemotherapy or immunosuppressive therapy. The median time from catheter insertion was 3.7 years (range 1.6 – 8.8 years). All patients developed pulmonary TB-BCG and two also developed a possible extra-pulmonary disease with

granulomatous hepatitis. Catheter cultures performed in three patients supported BCG catheter-infection. All patients required admission to four different hospitals in Barcelona. TB was treated with a combination of three or four drugs. Treatment duration ranged from 9 to 30 months.

Three patients were under TB treatment alone, without catheter removal. Treatment outcome was favorable in eight cases. One patient treated without catheter removal developed a relapse and was cured after catheter removal and re-treatment. Three patients died, after finishing tuberculosis treatment, due to causes not related to TB.

The microbiological and genetic study showed that all samples, recovered from patients, corresponded to the same BGC-OncoTICE® as the one used in the four outpatient settings to treat the bladder cancer in other patients⁵.

Conclusions

The present study shows the possibility of nosocomial colonization of permanent catheter with BCG and the subsequent systemic infection in patients who have not previously received intravesical BCG. This mechanism of BCG transmission has not been previously described. Several deviations from appropriate operating procedures in BCG management explain the cross-

contamination and the consequent development of TB due to BCG. This problem may be frequent around the world. Due to its high capacity for environmental persistence as a live agent, BCG should be handled with appropriate precautions.

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The SH-TBL Project: Study of TB lesions obtained in Therapeutical Surgery

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The SH-TBL Project is an ambitious project conducted by the Experimental Tuberculosis Unit in collaboration with the National Center for Tuberculosis and Lung Diseases (Tbilisi, Georgia), the Pathology Department of the Germans Trias i Pujol Hospital, and the UITB (Unitat d'Investigació en Tuberculosis de Barcelona). Registered in the ClinicalTrials.gov data base with identifier NCT02715271, and started in April 2015, the project has the aim to study the patients undergoing routine therapeutical surgery for their tuberculosis (TB) in Tbilisi. In Georgia, a TB high-incidence country (116/100.000 habitants)¹, therapeutical surgery is still used as treatment for TB in Georgia, as in other countries in Asia and Africa², for both Drug Sensitive and Multi or Extensively Drug Resistant TB (MDR/XDR-TB), to cope with TB complications and/or sequelae, and with overall good outcomes³.

The study has two phases or substudies: a retrospective study, already ended, and a prospective part. Both include the collection of data on clinical and epidemiological data, as well as on the histopathological characteristics of TB lesions. A total of 137 patients were included in the retrospective study, all those operated during years 2014 and 2015 in the NCTLD. The analysis of the results showed that in spite of not finding any causality due to gender, differences were encountered between men and women. A higher percentage of men were operated, and they had more comorbidities and complications associated to their TB. Women were operated at younger ages, and later; and showed higher percentages of fresh necrosis in surgical specimens, specially if MDR/XDR-TB cases. The main result of the study was that a non despicable percentage of cured cases using the WHO definition, showed viable *M.tuberculosis* when samples from surgical specimen were cultured. This suggest other correlators of sterilization rather than negativization of culture would be needed, and that the WHO definition of cure should be revised⁴.

The prospective study, currently ongoing, has already recruited 5 patients and besides the collection of clinical and epidemiological data, includes the collection of blood, urine and tissue samples from different parts of the resected lesions;

as well as the measurement of changes in Health Quality of Life of patients before and after the treatment. We are interested in the type of necrosis found in lesions, as a marker of negative or positive evolution. From the host side, we are collecting samples for immunological and host expression assays (gene and protein profiling). From the microbiological side, we are culturing samples from different parts of the resected specimens, in order to be able to detect any differences from the pathogen side, and according to their presence in different layers of the granuloma.

By gathering information on both the host and the pathogen, on the mechanisms associated to the generation and evolution towards active TB and prognostic biomarkers, we do expect to obtain enough data to be used for patients stratification and/or to design new therapeutic strategies.

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