Recurrent invasive pneumococcal disease (RIPD) in an immunocompromised patient

Enfermedad neumocócica invasora recurrente (ENIR) en un paciente inmunodeprimido

Dear Editor,

Currently, up to 105 capsular serotypes of *Streptococcus pneumoniae* have been described, but only a limited number of them produce the majority of cases of invasive pneumococcal disease (IPD).[1] IPD is a vaccine-preventable illness; the vaccines available to date in the region of Madrid have been the 23-valent pneumococcal polysaccharide vaccine (PPV23) since 2001, the 7-valent pneumococcal conjugate vaccine (PCV7) since 2004, and the 13-valent conjugate vaccine (PCV13) since 2010 in the private market, and since 2016 in the national pediatric schedule.[2] In our region, the incidence of IPD is 6.36 cases per 100,000 inhabitants.[3] In countries that also include conjugate vaccines (initially PCV7 and later PCV13), and with an IPD incidence rate comparable to ours, it has been estimated that approximately 1.8% of cases may experience a second episode of IPD.[4] Recurrent invasive pneumococcal disease (RIPD) is defined as the occurrence of two or more episodes of IPD in the same patient separated by an interval of at least one month in duration.[5,6] When the strain causing the episodes is the same, it is considered a relapse, and if the episodes are due to different strains, it is considered reinfection.[5]

In this clinical case, a 67-year-old patient with a diagnosis of RIPD is presented. The patient's clinical history included chronic kidney disease secondary to Sjögren's syndrome associated with treatment with immunosuppressive corticosteroids, chronic hepatitis B being treated with entecavir, and chronic obstructive pulmonary disease emphysematous type. In 2017, the patient was diagnosed with diffuse large B-cell lymphoma with plasmacytoid differentiation and showed a partial response to treatment. In 2018, the patient underwent an autologous hematopoietic stem cell transplant (aHSCT). The patient had been previously vaccinated before the transplant with a dose of PPV23 (November 2015) and another of PCV13 (December 2017). After the transplant, he was again vaccinated with a complete sequential schedule of three doses of PCV13 (February, March, and April 2019) and one of PPV23 (September 2019). Between October 2022 and January 2023, the patient experienced three episodes of IPD caused by different serotypes and different genotypes (associated with different Multilocus Sequence Typing [MLST] scheme sequence type [ST], clonal complex [CC], and genetic lineage [GPSC] patterns) (Table 1). The first episode was initially treated with ceftriaxone and was maintained after confirming the strain's sensitivity to the antibiotic. In the second episode, treatment was started with piperacillin/tazobactam; however, after obtaining the antibiogram results, which showed resistance only to erythromycin, treatment was adjusted to ceftriaxone. The last admission was the most severe, requiring ICU assistance with orotracheal intubation. Empirical broad-spectrum treatment was initiated and de-escalated to high-dose ceftriaxone after confirming by antibiogram resistance to erythromycin and susceptible with increased exposure to other antibiotics (Table 1). The patient fully recovered and was discharged.

Thus, the presented case involves an immunosuppressed patient, in whom a different serotype was identified in each episode of IPD, confirming reinfection. These episodes occurred over a span of 3 months, with a 2-month interval between the first (bacteremic pneumonia by serotype 31) and the second episode (bacteremia without focus by serotype 15B), but with only an 11-day interval between the second and the third episode (bacteremic pneumonia serotype 19A) (Table 1). The occurrence of this last episode in such a short period of time is quite striking. Reinfection is typically defined as the occurrence of consecutive episodes separated by at least one month.[5,6] However, in this case, the last two episodes of IPD were caused by different serotypes from completely different genetic lineages (serotype 15B ST193*/CC193/GPSC11, and serotype 19A ST17169/CC320/GPSC1). In the serotype 15B strain, a new *ddl* allele was identified in its MLST scheme, so is a single locus variant of ST193 still pending new ID assignment.

The patient was adequately vaccinated according to official recommendations for aHSCT patients[7] with the PPV23 pneumococcal vaccine (which includes the 15B and 19A serotypes identified in the second and third episodes) and also had received three doses of the PCV13 vaccine (which includes the 19A serotype identified in the third episode). Therefore, the second and third episodes were vaccine failures of PPV23, and the third episode was also a failure of PCV13.

The majority of patients suffering from RIPD have predisposing diseases.[6,8] However, between 25 and 30% of cases may lack this type of history.[4,8] RIPD can be particularly favored by immune system alterations that decrease the host's response to infection.[8,9] The rate of vaccine failures in children with a complete series of three doses of PCV13 in these cases has been estimated at 12%.[8] The occurrence of vaccine failures following immunization with conjugate vaccines has been observed,[4,10] and RIPD has been described in cases with lymphoma.[9]

Table 1
Description of admission, therapy, evolution, and microbiological results of the three episodes of invasive pneumococcal disease. Hospital Universitario 12 de Octubre.

Date of admission	ICU admission	Diagnostic imaging	Blood culture	Serotype	Genotype	Antibiotic sensitivity profile MIC (EUCAST criteria)				Treatment		
						Penicillin	Cefotaxime	Erythromycin	Levofloxacin	First treatment	Second treatment	Third treatment
30/09/22 to 03/10/22	No	X-rays: right-sided lung consolidation	*Streptococcus pneumoniae*	31	ST1766/ CC3548/ GPSC57	0.016 mg/L (S)	0.016 mg/L (S)	0.094 mg/L (S)	0.75 mg/L (I)	Ceftriaxone + azithromycin (1 tablet, 500 mg)	Ceftriaxone (1000 mg/24 h – 3 days)	
02/12/22 to 14/12/2022	No	X-rays: no pathological findings	*Streptococcus pneumoniae*	15B	ST193*/ CC193/ GPSC11	0.016 mg/L (S)	0.012 mg/L (S)	>256 mg/L (R)	0.38 mg/L (I)	Piperacillin/ tazobactam (4.00 mg/ 500 mg i.v. every 12 h)	Ceftriaxone (1000 mg/24 h i.v. – 10 days)	
25/12/22 to 13/01/23	Yes (from 25/12/2022 to 05/01/2023)	CT scan: Consolidation of the apical and posterobasal segments of the left lower lobe. Associated with partial filling with secretions from segmental bronchi of the left middle lobe, intermediate, and left lower lobe.	*Streptococcus pneumoniae*	19A	ST17169/ CC320/ GPSC1	2 mg/L (I)	1 mg/L (I)	>256 mg/L (R)	0.75 mg/L (I)	Piperacillin/ tazobactam (4.00 mg/ 500 mg – 1 vial)	Linezolid (600 mg/12 h i.v. for 48 h)	Ceftriaxone (2000 mg/12 h i.v. – 5 days)

*Serotype 15B strain presented a single nucleotide polymorphism in the *ddl* gene, being a single locus variant of ST193, and still pending an assignment of a new ID.
S, susceptible; I, susceptible with increased exposure; R, resistant.

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https://doi.org/10.1016/j.eimc.2024.06.004

Intolerancia a vía oral: nuevo escenario para la terapia antirretroviral parenteral

Oral intolerance: new scenario for parenteral antiretroviral therapy

Hasta la fecha, las guías de práctica clínica recomiendan iniciar y mantener tratamiento antirretroviral (TAR) en todos los pacientes con diagnóstico de infección por el virus de la inmunodeficiencia humana (VIH), independientemente de la cifra de Linfocitos T CD4, con la intención de mejorar su salud, reducir el estado proinflamatorio y disminuir la prevalencia de enfermedades asociadas, preservando o tratando de mejorar la función inmunológica, así como reducir la transmisión del VIH en la población[1].

Atendiendo a las recomendaciones previas, la cuestión es más grave cuando acontecen situaciones clínicas inesperadas que impiden mantener el TAR por vía oral. Para su abordaje, las guías de práctica clínica más recientes como las estadounidenses proponen soluciones temporales como la suspensión perioperatoria por menos de dos días, la secuenciación a formulaciones líquidas o a regímenes de TAR que se puedan triturar y sean compatibles para su administración por vías enterales[2]. Pero ¿qué sucede cuando la vía oral es totalmente inaccesible incluso empleando una sonda nasogástrica? Ante esta cuestión clínica, documentamos el siguiente caso clínico:

Paciente mujer de 55 años de edad, vive con VIH desde el año 2000. En su tercera línea de TAR: lo inició con darunavir potenciado con ritonavir y emtricitabina/tenofovir disoproxil fumarato (DRV/rito + FTC/TDF) que posteriormente se simplificó a dolutegravir/abacavir/lamivudina (DTG/ABC/3TC) y desde diciembre de 2020 simplificada a terapia dual en régimen basado en inhibidores de la transcriptasa inversa no análogos de nucleósidos (ITINAN) con dolutegravir/rilpivirina (DTG/RPV). No había presentado ningún fracaso virológico, pero no disponíamos de más información pues se había trasladado desde otro centro en el que se hizo el diagnóstico. Pese a no tener documentado estudio de mutaciones de resistencia, el TAR actual suscitaba la no sospecha de mutaciones en la retrotranscriptasa pues mantenía un adecuado control inmunovirológico en los seis meses previos al ingreso (Linfocitos T CD4: 501/mm^3 y carga viral VIH < 40 cp/mL) con un TAR basado en ITINAN.

Como otros antecedentes, destacaba una infección crónica por el virus de la hepatitis C (VHC) tratada y en respuesta viral sostenida sin datos de hepatopatía e inmunizada frente al virus de la hepatitis B (VHB). En septiembre de 2023, tras un síndrome consuntivo, ictericia y diarrea, es diagnosticada de adenocarcinoma de páncreas estadio IIB por lo que inició tratamiento quimioterápico neoadyuvante y en mayo de 2024, fue intervenida, realizándose una duodenopancreatectomía cefálica con resección parcial de la pared lateral de la vena porta con adecuada respuesta radiológica y biológica. El posoperatorio implicó un sondaje nasogástrico a caída libre que mantenía con un alto débito. El abordaje enteral no era una opción, pues todo el contenido oral era eliminado por la sonda nasogástrica y la cirugía no permitía otro abordaje intervencionista. Con ello y en previsión de que la situación persistiera durante un largo tiempo y tras haber transcurrido tres días de omisión del TAR oral previo, es donde surge la posibilidad de secuenciar el TAR a vía parenteral. Así se hizo, administrándose cabotegravir (CBG) + RPV por vía intramuscular, tras valorar riesgo/beneficio y en consenso con la paciente, que mantenía un adecuado control inmunovirológico. No presentó ningún efecto secundario derivado de ello.

Disponemos de algunos medicamentos antirretrovirales en formulaciones parenterales como zidovudina, enfuvirtida, ibalizumab, CBG y RPV. La combinación de acción prolongada CBG + RPV está aprobada como un régimen completo para el tratamiento del VIH e incluida como opción de simplificación en guías como la española de GESIDA en pacientes sin fracasos virológicos previos, sin mutaciones de resistencia conocidas ni sospechadas a integrasas ni a ITINAN, que, además, hayan mantenido supresión virológica en los seis meses previos con un TAR oral estable[3]. Aún no disponemos de evidencia científica suficiente como para su recomendación en situaciones como la descrita en este manuscrito[2,4–6].