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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Oral intolerance: new scenario for parenteral antiretroviral therapy

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

Clinical practice guidelines recommend starting and maintaining antiretroviral treatment (ART) in all patients diagnosed with human immunodeficiency virus (HIV) infection, regardless of the number of CD4 T lymphocytes, with the aim of improving their health, reducing the pro-inflammatory state and lowering the prevalence of associated diseases, preserving or trying to improve immune function, and reducing HIV transmission in the population.[1]

Based on previous recommendations, the issue is more serious when unexpected clinical situations occur that prevent oral ART from being continued. Under such circumstances, the most recent clinical practice guidelines, including those from the United States, propose temporary solutions such as perioperative suspension for less than two days, sequencing to liquid formulations or ART regimens that can be crushed and are compatible for administration via enteral routes.[2] But what happens when the oral route is totally inaccessible even using a nasogastric tube? We report the following case in response to this clinical issue.

Our 55-year-old female patient has been living with HIV since 2000. She was on her third line of ART: she was started with darunavir boosted with ritonavir and emtricitabine/tenofovir disoproxil fumarate (DRV/r + FTC/TDF) which was later simplified to dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) and, since December 2020, simplified to dual therapy in a regimen based on non-nucleoside reverse transcriptase inhibitors (NNRTI) with dolutegravir/rilpivirine (DTG/RPV). She had not suffered any virological failure, but we had no more information as she had been transferred from another centre where the diagnosis had been made. Despite not having a documented study of resistance mutations, the current ART raised no suspicion of mutations in reverse transcriptase as the patient maintained adequate immunovirological control in the six months prior to admission (CD4 T lymphocytes: 501/mm^3 and HIV viral load <40 cp/mL) with an NNRTI-based ART.

Her other previous medical history included chronic infection with the hepatitis C virus (HCV), treated and in sustained virologic response with no signs of liver disease, and she was immunised against the hepatitis B virus (HBV). In September 2023, after a wasting syndrome, jaundice and diarrhoea, she was diagnosed with stage IIB pancreatic adenocarcinoma, for which she began neoadjuvant chemotherapy and in May 2024, she underwent surgery, performing a pancreaticoduodenectomy with partial resection of the lateral wall of the portal vein, with adequate radiological and biological response. Postoperatively the patient had a nasogastric tube with free drainage, which was producing a high output. The enteral approach was not an option, as all oral contents were removed by the nasogastric tube and the surgery did not allow another interventional approach. Therefore, in anticipation of the situation persisting for some time and after three days of omission of the previous oral ART, we considered the possibility of sequencing to parenteral ART. We went ahead, administering cabotegravir (CAB) + RPV intramuscularly, after weighing up the risk/benefit and in consensus with the patient, who maintained adequate immunovirological control. She did not develop any related side effects.

There are some antiretroviral medications available in parenteral formulations, such as zidovudine, enfuvirtide, ibalizumab, CAB and RPV. The long-acting CAB + RPV combination is approved as a complete regimen for the treatment of HIV and is included as a simplification option in guidelines such as the Spanish Grupo de Estudio del SIDA (GESIDA) [AIDS Study Group] in patients without previous virological failures, without known or suspected resistance mutations to integrases or to NNRTI, who, in addition, have

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