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Conflict of interest

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Adverse Events Associated With New Injectable-Free Multidrug-Resistant Tuberculosis Drug Regimens

Efectos adversos asociados a los nuevos tratamientos farmacológicos sin inyectables contra la tuberculosis multirresistente

Dear Editor,

Multidrug-resistant tuberculosis (MDR-TB) represents a global challenge. In 2018, 186,772 new cases of MDR-TB or TB resistant to rifampicin (RR-TB) were notified globally, resulting in an estimated incidence of 484,000 (95% confidence interval 417,000–556,000).[1] Mathematical modelling studies estimate the number of MDR-TB in children as between 25,000 and 32,000 annually, although it is suspected that <5% are identified and even less are correctly treated.[2]

Treatment outcomes for MDR-TB remain suboptimal. In the last 40 years only two new drugs for TB treatment have been licensed (bedaquiline and delamanid).[3] However, the World Health Organization (WHO) has recently updated its guidelines on MDR-TB treatment, as well as the SEPAR guideline updated in 2017.[4,5] They propose new drug combination regimens which exclude the second-line injectable agents and include bedaquiline, delamanid and other repurposed drugs such as linezolid and clofazimine in order to optimize safety and efficacy.[4] Bedaquiline is considered highly effective and is recommended in all MDR-TB regimens for adults and children > 6 years; however, it is expensive and not currently available in many European countries such as Spain. Bedaquiline dosing and safety studies are yet to be done in young children (<6 years). Linezolid is also recommended as a core agent with good activity against *M. tuberculosis* including extensively drug-resistant (XDR) strains. Fluoroquinolones (levofloxacin and moxifloxacin) complete the group of the most effective agents (Group A).[4] The major advantage is that they are all-oral regimens, increasing treatment feasibility and reducing severe adverse events such as ototoxicity and nephrotoxicity caused by the aminoglycosides. However, these new drug regimens are not exempt from adverse events and data on safety and efficacy in children are scarce.[2] We present a case of probable cycloserine-associated behavioural disturbance with neuromuscular symptoms, as well as intracranial hypertension secondary to levofloxacin in a child with MDR-TB.

A previously healthy, not BCG-vaccinated, Spanish six-year-old girl was diagnosed with tuberculosis (TB) following active household contact tracing. Her father, diagnosed with infectious MDR pulmonary TB, was the index case.

At diagnosis she was asymptomatic, with normal physical examination and a positive tuberculin skin test (induration of 13 mm). Left hilar enlarged lymph nodes were suspected on her chest-X-ray and bilateral enlarged mediastinal and hilar lymph nodes with bilateral lung nodules were detected on chest computed tomography (CT) (Fig. 1). Serial gastric aspirate specimens for acid-fast bacilli smear microscopy, PCR and mycobacterial culture were negative in the patient; however, *M. tuberculosis* cultures were positive in both her father and four-year old brother, with isolates showing resistance to isoniazid, rifampicin, pyrazinamide, ethionamide and streptomycin. These findings were sufficient for the diagnosis of MDR pulmonary TB, reserving the bronchoscopy in the event that the patient did not have a known TB contact or antimicrobial sensitivity pattern. Therefore, an injectable-free treatment regimen was initiated with levofloxacin (18.5 mg/kg/day), linezolid (14 mg/kg/day), clofazimine (100 mg every second day), cycloserine (18.5 mg/kg/day) and ethambutol (18.5 mg/kg/day).

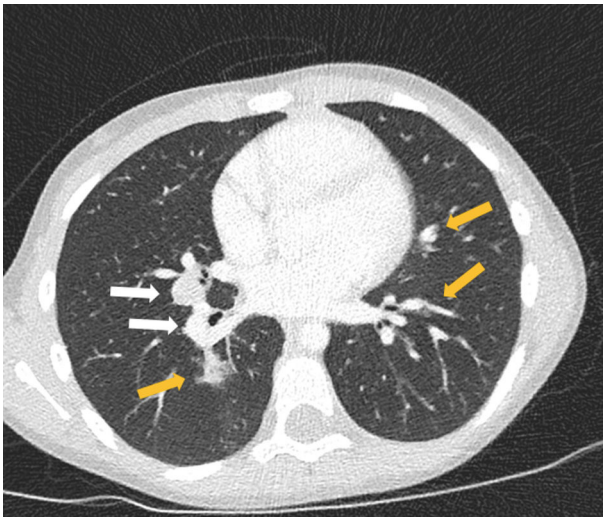

Fig. 1. Chest computed tomography scan showing lymph nodes (white arrows) and parenchymal opacities (yellow arrows).

Three weeks later, she was admitted to hospital due to vomiting and refusal to take MDR-TB drugs. On admission she presented with right-sided torticollis and an adjustment disorder with mixed disturbance of emotions and conduct including insomnia and an anxiety crisis. Six days later, the patient also developed right peripheral facial palsy. A cranial and cervical spine CT scan did not show any abnormal findings such as an intracranial tuberculoma or cervical spine TB. Complete blood count (CBC), renal, hepatic and mineral panel and thyroid function tests were normal. Rheumatoid factor and anti-nuclear antibodies were negative. Cycloserine was considered as likely responsible for these clinical findings and was discontinued: neuro-psychiatric symptoms progressively disappeared. Delamanid (4 mg/kg/day) was added to the treatment regimen to replace cycloserine.

Two weeks later (5 weeks after treatment initiation), bilateral optic disc swelling was detected after performing a routine ophthalmological toxicity examination. She was asymptomatic at this time and a brain magnetic resonance imaging showed a papillary protrusion and posterior flattening of both eyes (indirect signs of intracranial hypertension) without any other abnormal radiological findings. Cytological and biochemical analysis of the cerebrospinal fluid were normal and culture was negative. An increased intracranial pressure (ICP) (34 cm H_2O) confirmed the diagnosis of intracranial hypertension. Levofloxacin was considered the likely cause and was discontinued. To manage the raised ICP, acetazolamide was added, causing metabolic acidosis, which was treated with oral bicarbonate. Thereafter her clinical resolution was good with a progressive decrease of ICP and after six weeks the fundus examination returned to normal.

At present, she is in the 8th month of treatment and medications including linezolid, clofazimine, delamanid, and ethambutol are well tolerated. She remains asymptomatic presenting an adequate weight gain. Serial chest X-ray are normal and a chest CT will be scheduled at the end of treatment at 15 months from treatment initiation. Clinical follow up including CBC, electrocardiogram and ophthalmologic exam is performed on a monthly basis.

This case report shows the challenges of managing MDR-TB in children. The clinical evolution of this case with several adverse events related to the MDR-TB treatment, highlights the potential risk of adverse effects caused by these new drug combinations and the concern that treatment interruption may compromise treatment efficacy.

Initially, the patient presented with behavioural disturbance after three weeks of MDR-TB therapy. The association of cycloserine with depression, psychosis and neuropathy is well established.[3] Cycloserine-associated neuro-psychiatric effects are likely due to its binding to N-methyl-D-aspartate receptors and it has been demonstrated that these adverse events are related to high drug concentrations in serum. This has led to investigate the therapeutic use of cycloserine at lower doses for psychiatric disorders.[6] Therapeutic drug monitoring is used to individualize treatment doses and might help to prevent toxicities caused by high drug concentrations; however, it was not performed in this case as it was not locally available. Moreover, based on the presence of right-sided torticollis and lower motor neuron facial palsy, a space-occupying lesion was also ruled out. We finally attributed these neuro-psychiatric symptoms to cycloserine, as they progressively disappeared after the withdrawal of the drug.

The association between fluoroquinolones and intracranial hypertension has been previously described, although it is rare, and the pathogenic mechanism is not completely understood.[7] Few case reports have shown specific association of levofloxacin-induced intracranial hypertension between 5 days and 3 months after the start of the treatment.[8–10] We decided to discontinue levofloxacin and improvement of her condition was observed in a short period of time.

Fluoroquinolones are a key component for MDR-TB treatment. When contraindicated, the therapeutic strategy should be planned as extensively drug-resistant tuberculosis. Therefore, she eventually continued with a “non-optimal” regimen with good radiological response.

Despite the improvement in therapeutic strategies for MDR-TB, this case points out the need to keep searching for the most effective and least toxic drug regimen(s) for MDR-TB in children and in adults.

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COVID-19: new disease, new manifestations☆

COVID-19: enfermedad nueva, manifestaciones nuevas

To the Editor:

We report the case of a 66-year-old woman who was admitted to the pulmonology department in March 2020 for severe bilateral Covid-19 pneumonia. She had no previous respiratory history and had never smoked or been exposed to inhalants or environmental toxins. Her medical history was significant for dyslipidemia controlled by drugs, autoimmune thyroiditis that did not require treatment, and surgery for a benign breast tumor and cutaneous follicle center lymphoma with a negative extension study.

During the first 24 h after admission, her progress was poor, with clinical, radiological and blood gas deterioration despite treatment, so she was transferred to the intensive care unit (ICU). During her ICU stay, she required invasive mechanical ventilation and pronation maneuvers. Fever persisted, so antibiotic treatment (ceftriaxone, azithromycin, ceftaroline, piperacillin/tazobactam) was optimized and the Covid-19 therapeutic protocol (lopinavir/ritonavir, Betaferon® and hydroxychloroquine) was implemented. Dexamethasone was also added and a single dose of tocilizumab (400 mg) was administered. Biological parameters were significant for ferritin levels >15,000 ng/mL and IL-6 prior to tocilizumab 206 pg/mL. Finally, after a prolonged stay in the ICU, the patient improved and was discharged to the hospital ward.

Her subsequent respiratory progress was slow but favorable. Clinical improvement was associated with a progressive reduction in supplementary oxygen needs and improvement in all inflammatory parameters (PCR, LDH, ferritin, IL-6; CPK, D-dimer) and radiological infiltrates. At this time, we decided to initiate an inpatient rehabilitation program, progressively testing tolerance to sedation after prolonged admission.

However, despite improvement, the patient presented desaturation (up to SpO_2 90% with FiO_2 50%) coinciding with sedation, along with tachycardia, tachypnea, distal cyanosis, and intense dyspnea, whereas this clinical picture resolved completely when the patient was returned to decubitus (Fig. 1). The first episode of desaturation was accompanied by an intense syncopal syndrome, so an urgent study was requested to rule out an acute cardiac episode (the ECG showed a known right bundle branch block, while NTproBNP and ultrasensitive troponins were normal); CT angiogram was negative for pulmonary thromboembolism and deep vein thrombosis of the lower limbs. However, CT revealed numerous areas of ground glass opacity mainly in the subpleural region, especially abundant in the pulmonary bases, all associated with the resolving infectious process. In view of the clinical suspicion of platypnea-orthodeoxia syndrome (POS), an echocardiogram was requested with intravenous injection of agitated serum that showed no signs of intracardiac shunt or delayed passage of bubbles. POS finally resolved after several weeks of convalescence.

The pathophysiological factor underlying hypoxemia in POS is the shunt effect.[1] The causes associated with POS are classified as intracardiac and extracardiac (pulmonary) etiologies and a third heterogeneous group.[1] In lung diseases, shunt can be caused either by the mixture of arterial and venous blood (as in arteriovenous fistulas), or by a serious alteration of the V/Q ratio,[2] such as occurs in some parenchymal diseases. Gravity increases blood flow to the pulmonary bases, while perfusion pressure decreases in apical regions (dead space effect in the apex). This vascular redistribution contributes to increasing the differences in the V/Q ratio that are especially noticeable in a standing position.[3] Thus, the development of POS associated with emphysema, interstitial diseases and consolidations has been described, particularly when the basal parenchyma is involved.[4] Pulmonary alterations typical of adult acute respiratory distress syndrome (ARDS) would also be included within this definition.

The data analyzed so far suggest that the new coronavirus demonstrates particular tropism for the vascular endothelium. SARS-CoV-2 initiates cellular infection by binding to the angiotensin-converting enzyme receptor II that is widely distributed throughout the body, including the endothelium. Some autopsies have shown viral inclusions in endothelial cells with accumulations of inflammatory cells, findings that are suggestive of endothelitis.[5] Thus, endothelial activation induced by the virus can result in both thrombotic phenomena and marked vasodilatation. In the lungs, vasodilation and endothelial dysfunction aggravate the shunt effect observed in some patients.[6] In a review of radiological manifestations of Covid-19 detected on CT, dilation of pulmonary vessels, especially those closest to or within ground glass areas, was frequently observed.[7] This phenomenon appears to be directly related to the production of inflammatory mediators, especially IL-1 and IL-6, cytokines that have been shown to have a potent vasodilator effect *in vivo*.[8] Vasodilation induced by both inflammatory mediators and direct viral endothelial damage could cause the shunt effect.

The interest in this case lies not only in the rarity of POS, but in its association with SARS-CoV-2 infection. Cases of POS associated with infectious agents during the convalescence period following an episode of ARDS caused by *Pseudomonas aeruginosa*[9] and *Pneumocystis jirovecii* and cytomegalovirus pneumonias[10] have been reported, and it has also been described in ARDS associated with non-infectious agents such as antisynthase syndrome.[11] However,

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