respectively, undetectable haptoglobin levels and negative Coombs test in both cases. In the face of suspected haemolytic anaemia secondary to artemisinins, and once haemoglobinopathies had been ruled out, treatment was started with prednisolone at 1 mg/kg/day for 3 days with good clinical and lab test evolution although one of the patients, the older sister, required a packed red blood cell transfusion due to haemoglobin of 6.3 g/dL.

A 6-year-old boy is transferred to our site with a diagnosis of malaria due to *P. falciparum* and *Plasmodium vivax* in light of the need for intensive care (parasitaemia 25%). There was history of a recent extended stay in Gambia, without antimalarial prophylaxis. At his site of origin he was treated with proguanil/atovaquone, with a poor clinical and lab test response at 24 h after admission. In ICU he was treated with cefotaxime and intravenous artesunate (2.4 mg/kg dose, 0.12 and 24 h) followed by piperaquine-artenimol 3 days with a favourable response. At 8 days of evolution haemolysis findings were detected: haemoglobin of 7.5 g/dL (drop of 2 g/dL compared to previous follow-up, 9.9 g/dL) was detected, hyperbilirubinaemia of 2.08 mg/dL (previous follow-up 1.5 mg/dL), elevation of LDH to 1831 IU/L (previous follow-up 354 IU/L), undetectable levels of haptoglobin and positive Coombs test), haemoglobinopathies test within normal range. In the face of suspected haemolytic anaemia secondary to artemisinins, prednisolone was started at 1 mg/kg/day for 3 days with favourable clinical and lab test evolution.

Artemisinin derivatives have become the first-line option for the treatment of severe malaria. Their most common side effects are mild, although haemolytic anaemia secondary to their use has also been described, with an estimated incidence of between 7–21% of cases treated with an intravenous artesunate, especially in patients with a higher degree of parasitaemia,[4] although cases of haemolysis associated with treatment with oral artemisinins have also been described.[5] It usually appears between the first and fourth weeks after the start of its administration, and it is a different process from blackwater fever associated with treatment with quinine, which usually appears earlier.[6] The ultimate cause of haemolysis is unknown, although several hypotheses have been put forward. One of these is the removal at the splenic level of the previously infected red blood cells, with inclusion bodies, due to the phenomenon of «pitting».[7,8] An immune mechanism has also been put forward, since in some patients a positive Coombs test has been observed,[9] such as the third case presented, and a favourable response to corticosteroids, although the role of this therapy has not been clearly established.[10] Other approaches have also been posed, such as direct toxicity of an artesunate metabolite, dihydroartemisinin. There are also factors that favour a greater individual predisposition, such as haemoglobinopathies (sickle cell disease or glucose-6-phosphate dehydrogenase deficiency) or due to interindividual variability in drug metabolic pathways.

Haemolytic anaemia is a potential complication associated with treatment with intravenous artesunate in paediatric patients, for which reason its appearance must be monitored for during the weeks following its administration, especially in patients with high parasitaemias.

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Severe bradycardia probably associated to Oseltamivir in a pediatric patient with acute renal injury

Bradicadia severa probablemente asociada a Oseltamivir en un paciente pediátrico con fracaso renal agudo

Dear Editor,

Children constitute a high-risk population for the development of severe influenza regarding adult population. Current recommendations state that antiviral treatment should be provided to all children hospitalized with influenza or underlying medical conditions or those suffering from a severe illness.[1] Oseltamivir, a neuraminidase inhibitor (NI), represents the most widely used antiviral in children with influenza viral infection. We report a 10-year-old previously healthy female admitted to our PICU due to an acute kidney injury (AKI) (creatinine clearance < 30 ml/min/1.73 m^2), anemia (7.9 g/dl) with schistocytosis of 3.5% and thrombocytopenia (29,000/mm^3). She was conscious and did not require respiratory or hemodynamical support (SpO_2 100%, blood pressure 107/68 mmHg and heart rate (HR) 110 bpm).

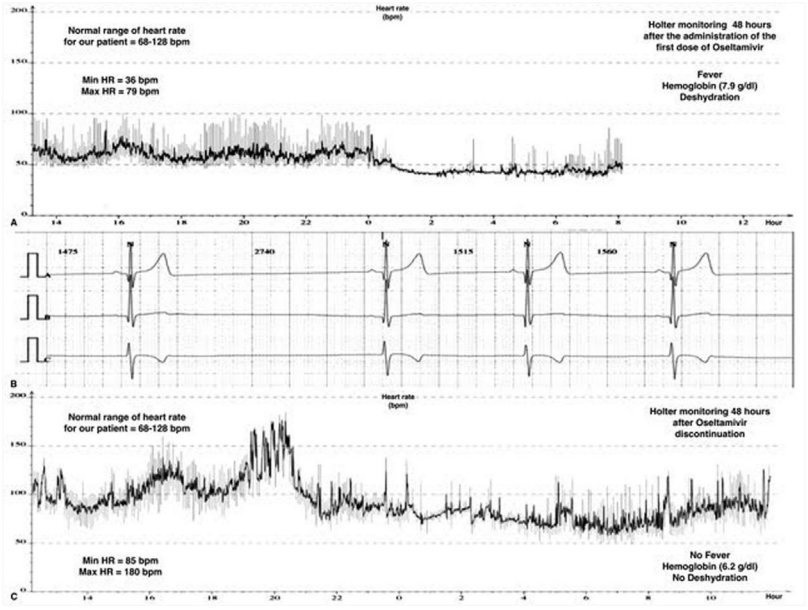

Fig. 1. Cardiac rhythm monitoring of our patient. Panel A is the record of the HR variability during the first Holter performed the third day of treatment with Oseltamivir, showing a severe bradycardia for age. Panel B is a capture of the cardiac monitor of the patient the first day of treatment with Oseltamivir, showing a sinus bradycardia (30–50 bpm). Panel C is the record of the HR variability during the Holter performed after 48 h of the discontinuation of Oseltamivir, showing a complete recovery of normal HR for age.

She was diagnosed as hemolytic-uremic syndrome (HUS), and supportive treatment with intravenous fluid therapy, blood products, omeprazole and acetaminophen was started. The patient presented flu-like symptoms from the previous 48 h, and in the etiological work-up study for HUS, a FilmArray Respiratory Panel detected H1N1 Influenza A as the trigger agent. We considered this clinical picture as a severe manifestation of the influenza virus infection, so treatment with oral Oseltamivir 30 mg od. (adjusted for AKI) was initiated. Twelve hours after the first dose we noticed a severe bradycardia on the cardiac monitor, with HR ranging from 30 to 57 bpm with a normal blood pressure (Fig. 1). The patient also started with vomiting but did not presented cardiac complaints. Serial ECG records showed sinus bradycardia and nodal rhythm with maximal HR of 60–70 bpm without other ECG abnormalities, including a normal QTc interval (400 ms). The 3rd day of treatment, a 24-h-Holter monitoring was performed evidencing a mean HR of 53 bpm, maximal 85 bpm and minimal 36 bpm, with 124 documented episodes of bradycardia regarding her age. Remarkably, the patient still presented severe anemia (hemoglobin of 6.2 g/dl), fever and clinical signs of dehydration at the time of this Holter monitoring. Cardiac biomarkers (hs-cTnT and NT-proBNP), thyroid function, chest X-ray and echocardiogram resulted in normal. Since she did not manifest cardiac symptoms, we decided to complete 5 days with Oseltamivir at same doses. Twenty-four hours after its withdrawal, we noticed a gradual recovery of HR up to normal values for age, that was confirmed with a new Holter monitoring. Oseltamivir seems to be an effective and well-tolerated therapy for acute influenza A and B infection in children. Nausea and vomiting, usually of mild–moderate intensity and short duration, are the most frequent side effects observed in children.[2,3] Severe adverse reactions such as neuropsychiatric are less frequent.[4] Although infrequent, cardiac adverse effects associated with Oseltamivir have been previously described in both animals and humans. In concrete, the development QTc interval prolongation and bradycardia seems to be closely related to the rapid increase of Oseltamivir carboxylate in plasma concentrations, even at first dose.[5] Some facts make it possible for bradycardia to be associated with Oseltamivir in this case. Occasionally, bradyarrhythmias are the prominent feature in influenza infection due to acute myocarditis, that could be misinterpreted as drug-related adverse events.[6,7] However, myocarditis and other secondary causes of bradycardia such as medications were ruled out in our patient. Also, there was a reasonable temporal sequence association between Oseltamivir administration and the appearance of bradycardia, which occurred even in the presence of concurrent causes of tachycardia. Finally, based on a Naranjo adverse drug reaction probability scale value of 5–6 points, bradycardia was considered as a probable side effect of Oseltamivir in our patient.[8] Due to the increasing use of Oseltamivir in children, pediatricians must be aware of its possible severe adverse effects. This is especially important in those patients with cardiac or renal comorbidities who are indeed more likely to receive this medication. Oseltamivir is exclusively eliminated by renal excretion, and the dose should be adjusted with creatinine clearance < 30 ml/min/1.73 m^2. Although there was no hemodynamics repercussion in our healthy patient, bradycardia could be an adverse event with potentially severe consequences in patients with heart diseases. Therefore, we consider that cardiac monitoring should be warranted during Oseltamivir therapy in those high-risk patients.

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Disseminated *Mycobacterium scrofulaceum* infection in a patient in treatment with golimumab☆

Infección diseminada por

Mycobacterium scrofulaceum (M. scrofulaceum) belongs to the nontuberculous mycobacteria group, with common presentation as cervical lymphadenopathy in infancy.[1] There are only a few cases of disseminated infection described to date, for which reason we present below the case of an immunocompromised adult.

A 38-year-old male is diagnosed with psoriatic arthropathy and had been being treated with golimumab for 2 years (he had previously received etanercept and adalimumab). He attended due to general malaise, headache, cough and a fever of 39° with no response to outpatient antibiotics. In the physical examination he presented with nuchal rigidity for which reason, in light of a normal brain computed tomography (CT), a lumbar puncture was conducted with cerebrospinal fluid compatible with lymphocytic meningitis, with 12 leukocytes/mm^3 (100% mononuclear), glucose 67 mg/dl, proteins 28 mg/dl and ADA 1.7 u/l. In ordinary culture, Lowenstein and multiple PCR of the cerebrospinal fluid were negative. In light of mediastinal widening on the x-ray, a CT was performed, with pulmonary micronodules, mediastinal and mesenteric lymphadenopathies, and splenomegaly, findings suggestive of miliary tuberculosis (Fig. 1). Following a bronchoscopy with biopsy of right paratracheal adenopathy empiric antituberculosis treatment was started (isoniazid, rifampicin, pyrazinamide and ethambutol) pending microbiological results. The node biopsy revealed necrotising epithelioid granulomas with presence of acid-fast bacilli, but in the culture material *M. Scrofulaceum* was isolated sensitive to all tested antibiotics, so antibiotics were adjusted to clarithromycin, rifampicin and ethambutol. This germ was not isolated in blood or cerebrospinal fluid.

The patient presented with good tolerance to treatment. A CT at 6 months demonstrated practical resolution of the lymphadenopathies and pulmonary micronodules, and after completing 12 months of treatment the patient is currently asymptomatic.

Atypical or nontuberculous mycobacteria are frequently found in the environment, especially in water. They are usually transmitted by inhalation or direct inoculation, they do not spread from person to person and they do not usually cause disease in immunocompetent subjects.[2] More than 150 species have been described, and within these *M. scrofulaceum* represents just 2.2% of these infections. Their typical form of presentation is cervical lymphadenitis or scrofula in infancy, followed by slowly growing cavitary pneumonia, more common in the elderly and those with chronic lung disease.[1] Disseminated *M. scrofulaceum*infection is exceptional. Since the first report in 1971[3] we have found only 10 cases described in the literature, 6 of these in adults: one patient had an HIV infection,[4] 2 leukaemia,[3,5] in another the immunological situation was unknown[6] and the other 2 did not have known immunodeficiency, except mild lymphopaenia in one of them.[1,7]

Our patient was also immunosuppressed due to chronic treatment with golimumab. This is an anti-tumour necrosis factor (anti-TNF) monoclonal antibody, which acts by decreasing the immune response through blocking this proinflammatory cytokine. It is employed in diseases such as rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. However, due to its action on the immune system, it can increase the risk of bacterial infections, infections by mycobacteria (mainly tuberculosis but also atypical), or opportunistic/invasive fungal infections.[8] As with other anti-TNFs cases of reactivation of latent tuberculosis have been described with the use of golimumab,[9] so it is essential to rule out this possibility and treat it if necessary, before starting treatment with this drug. In our patient, latent tuberculosis infection was ruled out by a Mantoux test (0 mm) before starting treatment. The risk of infection by nontuberculous mycobacteria is also heightened in patients treated with anti-TNF, most often by *M. avium complex*.[10] However, we have not found any described cases of infection by *M. scrofulaceum* in the literature to date associated with the use of golimumab, nor with other anti-TNFs.

Regarding treatment, just as with TB, discontinuation of the anti-TNF drug is recommended while treating the infection. Regarding antibiotic treatment, the regimen to be followed is not protocolised and neither is its duration. Given that *M. scrofulaceum* demonstrates higher rates of resistance that other mycobacteria[1] combination therapy guided by antibiogram is recommended for at least a year,

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