

Pseudotumor cerebri associated with cyclosporin use following renal transplantation

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ABSTRACT

Pseudotumor cerebri (PC) is a syndrome characterized by the presence of intracranial hypertension (ICH) and no alteration in the ventricular system. Renal transplanted patients seem more susceptible to develop it due to immunosuppressive therapy. Cyclosporin (CsA) is a rare cause of PC, scarcely reported in the literature, and should be considered in the differential diagnosis of ICH and papilledema in those patients. We report the case of a 10-year-old boy, with a renal allograft for three years, on chronic use of mycophenolate mophetil (MMF), CsA, and low doses of prednisone. The patient presented with headache, vomiting, diplopia, and photophobia. Funduscopy showed bilateral papilledema. Cerebrospinal fluid analysis and imaging tests were normal. After excluding secondary causes, PC was diagnosed based on the chronic use of CsA, which was then replaced by sirolimus. After that, the patient progressively improved, and the papilledema resolved in three months.

Keywords: pseudotumor cerebri, cyclosporin A, renal transplantation.

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INTRODUCTION

Pseudotumor cerebri (PC) is a syndrome characterized by the presence of intracranial hypertension (ICH, intracranial pressure > 200 mm H₂O) with normal cerebrospinal fluid composition and lack of intracranial lesion. It manifests mainly with headache, nausea and vomiting, a reduction in visual acuity, and diplopia.¹ Its occurrence in patients undergoing transplantation has been mainly reported after bone marrow transplantation, and more rarely in patients with renal allograft.^{2,3}

Cyclosporin (CsA) is an immunosuppressor that reversibly inhibits both autoimmune and allogeneic T-cell-mediated immune responses. That drug revolutionized organ transplantation, prolonging the survival of renal allografts. In up to 35% of the cases, the use of CsA may lead to neurological complications,² such as PC. Pseudotumor cerebri was first described in the past two decades and is rarely reported.³

We report a case of PC secondary to the use of CsA after three years of renal transplantation, which evolved satisfactorily, with no visual sequelae after drug suspension.

CASE REPORT

The patient is a 10-year-old male from the city of Doutor Severiano, in the Brazilian State of Rio Grande do Norte, on hemodialysis for four years because of nephrotic syndrome due to focal segmental glomerulosclerosis. The patient underwent renal transplantation with live donor (mother) in October 2004. He was immunosuppressed with mycophenolate mofetil (1 g/day), CsA (200 mg/day), and prednisone (5 mg/day), and the allograft function and

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evolution were excellent (creatinine = 0.7 mg/dL). The patient has a history of encephalitis due to varicella and cystitis due to CMV 30 days and nine months after renal transplantation, respectively.

The patient was admitted to our service of renal transplantation in August 2007 complaining of intense holocranial pulsing headache for a week, associated with vomiting, intense retroocular pain, diplopia, and photophobia. On physical examination, the patient was in regular general condition, aware, oriented, slightly pale, dehydrated (++)/IV, eupneic, afebrile, eutrophic, anicteric, acyanotic, and appeared to be in pain. His heart rate was 94 bpm. His cardiac and pulmonary auscultation, and abdomen and neurologic examinations were within the normal range, including the extrinsic eye musculature.

On ophthalmic examination, his distant visual acuity in both eyes was 20/40 with no correction. The biomicroscopy was within the normal range. The pupillary reflexes (direct and consensual) showed no alteration. Intraocular pressures were 10 mm Hg and 12 mm Hg in the right and left eyes, respectively. Funduscopy revealed bilateral papilledema, with no exudates (Figure 1). Ocular ultrasound confirmed papilledema with suggestive signs of neither intra- nor retroorbital masses. Campimetry was normal.

On hospital admission, laboratory tests were as follows: creatinine = 1.19 mg/dL; urea = 43 mg/dL; hemoglobin = 10.5 g/dL; hematocrit = 31.5%; leukocytes = 8000/mm³; 62% segmented neutrophils; 25% lymphocytes; platelets = 304,000/mm³; sodium = 134 mEq/L; and potassium = 4.1 mEq/L. In view of the possibility of an expanding intracranial process, cranial magnetic resonance imaging was performed and evidenced no structural alteration (Figure 2). The cerebrospinal fluid was limpid, revealing the following: leukocytes = 4 (80% mononuclear cells and 20% multinucleated cells); chlorine = 126 mEq/L; glucose = 70 mg/dL; protein = 26.6 mg/dL. Its pressure was within the normal range. Cultures and investigation for toxoplasmosis, tuberculosis, syphilis, neurocysticercosis, cryptococcosis, and cytomegalovirus in the cerebrospinal fluid were negative. On admission, cefepime and amphotericin B were initiated, but, as the complementary exams showed no evidence of infection and the renal function worsened (creatinine = 1.95 mg/dL), both drugs were discontinued after six days of use.

Despite the analgesia, the patient persisted with daily headache, ocular complaints, and sporadic vomiting. Funduscopy maintained the same previous pattern. The presence of papilledema and symptoms

of ICH, with a normal imaging exam, suggested PC secondary to the use of CsA. The serum level of the drug was 136 ng/mL, while the expected range for the patient's age was from 80 to 100 ng/mL. The suspicion of PC led to suspension of CsA and introduction of therapy with sirolimus.

The symptoms progressively improved, with resolution of the headache two days after the therapeutic change and introduction of dexamethasone. The patient was discharged from the hospital after two weeks with a significant improvement of his visual complaints and renal function. After three months, complete resolution of the papilledema was observed.

DISCUSSION

We report a case of PC in a patient with renal allograft, secondary to the chronic use of CsA, which evolved satisfactorily after drug discontinuation.

Figure 1. Eyegrounds showing bilateral papilledema.

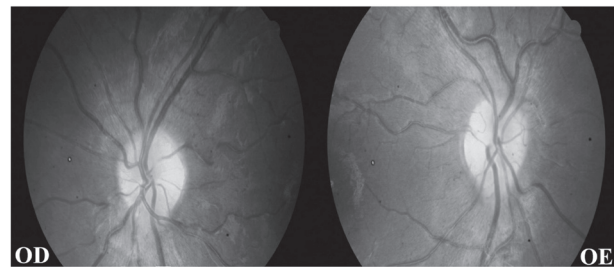
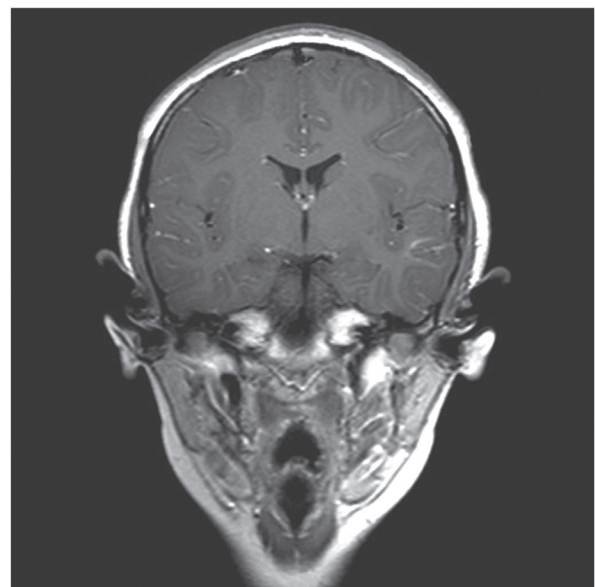


Figure 2. Magnetic resonance imaging of the skull showing no alterations.



Pseudotumor cerebri is a syndrome characterized by the presence of ICH with normal cerebrospinal fluid findings and no intracranial expanding process on imaging tests.⁴ It is idiopathic in most cases, but, when a probable diagnosis is considered, subjacent causes should be investigated. There are several etiologies and associated factors, such as recent weight gain, infections, endocrine changes, cranioencephalic trauma, and uremia. Medicamentous causes include chronic therapy with corticosteroids or their discontinuation, ingestion of high doses of vitamin A, citarabine, levothyroxine, danazol, amiodarone, and antibiotics, such as tetracycline, minocycline, ciprofloxacin, nalidixic acid, nitrofurantoin, and penicillin.⁵

For two decades, CsA has been reported as one cause of PC, especially following bone marrow transplantation.^{3,6,7} There are few reports of PC in patients on CsA after renal transplantation, despite the large number of renal transplantations performed each year.^{2,8-12} Those patients are at higher risk to develop PC, due to corticotherapy, anemia, hypercoagulability state, and weight gain.^{10,13,14} This fact seems confirmed by the high incidence of PC after renal transplantation, which may reach 5.4% in some services.^{10,12,14} A study by Francis¹² showed no time relation between the development of the disease and the date of surgery in children, PC occurring four months to seven years after renal transplantation (mean of four years). All patients affected were on CsA.

The pathogenesis of PC is still unknown, but it seems to involve some mechanisms, such as cerebrospinal fluid hypersecretion or absorption reduction, cerebral edema, and elevation in the cerebral venous pressure.^{3,5,12,15,16} Cyclosporin seems to cause neuro- and microvasculopathy with optic nerve damage and papilledema. In the presence of low serum concentrations, an idiosyncratic effect has been reported.^{6,9,17}

The clinical manifestations result from ICH. In the study by Phillips⁸, the following symptoms were found at presentation: headache (86%); nausea (46%); decrease in visual acuity (37%); vomiting and fatigue (31%); diplopia (29%); transient visual obscuration (20%); strabismus and photophobia (9%); and pulsatile tinnitus (6%). Papilledema occurs in 48% to 100% of the cases, can be asymmetric, and its severity is proportional to visual loss.¹⁶ It is worth emphasizing that the presence of optic disk edema due to chronic arterial hypertension, uremia, and diabetes mellitus may hinder the diagnosis of PC.¹⁴

Neurological effects secondary to the use of CsA may occur in 0.5% to 35% of the patients and comprise trembling, paresthesias, paralyses,

confusion, lethargy, depression, anxiety, insomnia, hallucinations, convulsions, aphasia, mutism.^{2,18} Headache is a common complaint and may end up simulating migraine and hypertensive encephalopathy. Thus, attention should be paid to unspecific complaints, especially when accompanied by visual alterations.

Neuroimaging, magnetic resonance imaging being the exam of choice, shows neither masses, nor ventriculomegaly, nor structural alterations. Venography through magnetic resonance imaging may be performed to exclude cerebral venous thrombosis. Aspiration of cerebrospinal fluid should be performed after excluding expanding lesions, and is crucial for the diagnosis of PC, in which case it shows normal cellularity and biochemistry tests. Aspiration of cerebrospinal fluid should be performed with the patient in the position of lateral decubitus and lower limbs relaxed to allow measuring its pressure, which in children is considered elevated when above 200 mm H₂O.⁵ Fluctuations in the cerebrospinal fluid pressure may justify normal manometries, despite the high clinical suspicion, as in the present case.^{19,20}

The basic indications for therapy include the presence of progressive visual loss, headache refractory to symptomatic treatment, and papilledema leading to axonal damages or optic nerve infarction. The basic treatment consists in reducing the CsA dose or drug replacement, with consequent improvement in visual acuity and decrease in intracranial pressure after some months. However, if the renal allograft cannot be maintained without the use of that immunosuppressive agent, optic nerve sheath fenestrations can be performed to avoid visual loss.^{5,8,13} If the renal function allows, carbonic anhydrase inhibitors can be used.^{1,5}

We report a case of PC in a 10-year-old boy secondary to the use of CsA three years after renal transplantation. Following CsA discontinuation, clinical improvement was observed with resolution of the papilledema after three months. It is worth emphasizing the importance of including the use of CsA in the differential diagnosis of ICH with no apparent cause in patients submitted to transplantation, thus avoiding diagnosis delay and sequelae.

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