VERY EARLY MENINGOENCEPHALOPATHY ASSOCIATED WITH THE INTRAOPERATIVE USE OF OKT3 IN RENAL RETRANSPLANT

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Muromonab CD3 (murine monoclonal antibody towards the cluster of differentiation 3 antigen; OKT3) is a murine IgG_{2a} monoclonal antibody from the OKT series that specifically reacts with the epsilon chain of the CD3 molecular complex on the surface of circulating T lymphocytes. OKT3 can be used as a treatment for acute allograft rejection episodes and as "rescue" therapy for steroid-resistant allograft rejection[1-7]. OKT3 can also be used during the perioperative period as induction therapy in sequential immunosuppressive regimens. Recently, OKT3 has elicited renewed interest due to its capacity to induce immune tolerance. This aspect will probably lead to the revaluation of OKT3 role for organ transplants[1].

We report a patient who received intraoperative inductive OKT3 in renal retransplant to improve graft viability. The patient developed a very early aseptic OKT3-related meningoencephalopathy that complicated her management during the immediate postoperative period. We were unable to find in literature such early onset of meningoencephalopathy associated with use of OKT3.

CASE

A 26-year old female with end-stage renal failure of undefined cause was admitted for cadaveric renal retransplant. She was on hemodialysis since 1990 and underwent to an unsuccessful renal transplantation in 1993.

Short before surgery hemodialysis was optimized in order to minimize CRS. Surgery started 19:00. Midazolam (15 mg) was used as anesthetic premedication. General anesthesia was induced with etomidate (0.2 mg/kg), sulfentanil (1 mg/kg) in bolus followed by atracurium (0.5 mg/kg) that was repeated every 30 minutes**.** She received epidural analgesia with bipuvocaine plus dimorphine. Anesthesia was maintained with O_2/N_2O [1:1] and isofluorane (concentration up to 1%) under controlled mechanical ventilation. Patient was monitored according with ASA recommendations. Inductive immunosuppressive therapy (sequential therapy) was applied through intravenous intraoperative use of 500 mg of methylprednisolone, followed by 5 mg OKT3 one hour later. These drugs were used before allograft perfusion. The surgery ended at about 23:00 h and all surgical and anesthetic procedures occurred without abnormalities. At about 01:15 h the patient presented fever (37.6ºC). During the next hours her body temperature ranged from 37.6 to 38.5ºC, while arterial pressure was stable, and arterial oxygen saturation ranged from 97% to100%, with O_2 administered through a Venturi mask. Since recovery from anesthesia was quite delayed, blood tests were ordered and she was admitted into the intensive care unit, where she was seen by a neurologist.

Upon this first neurological evaluation she showed response only to vigorous physical stimuli. She presented nuchal rigidity and had miotic pupils, but normal oculocephalic reflexes. Generalized hypertonia was evident and deep tendon reflexes were briskly symmetrical. Bilateral Babinski's sign was present. At this time urea was 94 mg/dL, creatinine was 5.5 mg/dL, hemoglobin was 9.4 g/dL, hematocrit was 26.7%. Other blood tests were all within normal range. CT scans revealed mild brain swelling. A lumbar tap was performed. The CSF aspect was mildly yellowish and opening pressure was 330 mmH_2O. Protein was 90 mg/dL, glucose was 75mg/dL, and white blood cell count was 386 cells/mm^3 (92% neutrophils, 8% mononuclear). Gram stain of the CSF and cultures were all negative. In spite of lack in literature of complications associated with intraoperative use of OKT3, we suspected of aseptic meningitis and encephalopathy related to the use of intraoperative OKT3 and decided not to administer

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any antibiotic therapy. During the subsequent two days the patient was managed only with supportive care. Her consciousness level gradually improved and the patient showed progressive recovery of muscle strength followed by normalization of her neurological exam. OKT3 was not discontinued and it was used for 10 days (2.5 mg/kg/day iv), associated to methylpredisolone (250 mg iv/day) that was used for 2 days after transplantation and then replaced by prednisone. Azathioprine was initiated during the third postoperative day because of neurological complications. Cyclosporine was delayed and initiated during the 7th postoperative day when creatinine level was 3 mg/dL. No further complication occurred and her kidney transplant was highly successful. No abnormal neurological deficit was observed at later neurological evaluations.

DISCUSSION

Aseptic meningitis and encephalopathy are considered complications of OKT3 use and it has been described earlier. The time for the occurrence of the first symptoms of OKT3-related meningoencephalopathy is variable. The syndrome is usually evident after 72 hours[8]. Eventually it may appear as early as during the first day of OKT3 use or as late as 30 days after the first exposure to OKT3[9]. However, we were not able to find in medical literature a very early onset impairing recovery from anesthesia as reported here.

The mechanisms involved in CNS adverse effects have not yet been completely elucidated. OKT3-induced T-cell activation with cytokines release[8], brain edema caused by capillary leakiness, cross-reaction of OKT3 with surface antigens shared by lymphocytes and CNS cell, and alteration in blood viscosity are all possible mechanisms involved[10]. Usually CNS signs and symptoms subside without specific interventions and without the need to discontinue OKT3 administration. However, CNS adverse effects can be severe enough to require discontinuation of OKT3 and to produce potentially hazardous neurological abnormalities[11].

Cadaveric renal transplantation, delayed graft function and diabetes have all been reported to be associated with OKT3-induced meningoencephalopathy[12]. In our case, pharmacological interaction of OKT3 with other drugs used during intraoperative period may have facilitated the development of meningoencephalopathy. Thus, identifying a potential pharmacological interaction of OKT3 with drugs used for anesthesia, as well as other additional intraoperative risk factors for the development of this syndrome would permit the optimization of the intraoperative use of OKT3, not only for kidney transplant but also for other types of transplants.

Like us, other authors have also reported diagnostic problems caused by perioperative use of OKT3[11]. Thus, in spite of its rarity, early postoperative CRS-related meningoencephalopathy must be considered as a possible differential diagnosis in all cases of abnormal anesthesia recovery or in those cases of early aseptic menigoencephalopathy seen in transplanted patients who receive intraoperative or perioperative OKT3.

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