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CASE REPORT

Matteo Cescon
Gian Luca Grazi
Roberto Assietti
Alberto Scanni
Franco Frigerio
Francesca Sparacio
Giorgio Ercolani
Antonino Cavallari

Embryonal rhabdomyosarcoma of the orbit in a liver transplant recipient

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M. Cescon (✉) · G.L. Grazi · G. Ercolani
A. Cavallari
Department of Surgery
and Transplantation, Policlinico S. Orsola,
University of Bologna, Via Massarenti 9,
40138, Bologna, Italy
E-mail: glgrazi@unibo.it
Tel.: +39-051-6364823
Fax: +39-051-304902

R. Assietti
Division of Neurosurgery,
Ospedale Fatebenefratelli e Oftalmico,
Milan, Italy

A. Scanni
Division of Oncology and Chemotherapy,
Ospedale Fatebenefratelli e Oftalmico,
Milan, Italy

F. Frigerio
Division of Radiotherapy, Ospedale S.
Gerardo, Monza, Italy

F. Sparacio
Operative Unit of Pathology, Ospedale
Fatebenefratelli e Oftalmico, Milan, Italy

Abstract Although an increased incidence of de novo malignancies is reported in transplant recipients, rhabdomyosarcoma, an aggressive mesenchymal tumor typical of childhood, is not considered a neoplasm commonly related to immunosuppression. A 21-year-old woman presented with unilateral diplopia and proptosis 16 months after liver transplantation for fulminant hepatic failure. A tumoral mass originating from the medial rectus muscle was partially removed and diagnosed as being an embryonal rhabdomyosarcoma. Since the patient refused complete orbital excision, one course of radiotherapy and six courses of chemotherapy were administered, while immunosuppression was re-modulated, without interruption of the administration of cyclosporine. Complete control of tumor growth was achieved, while no alterations of graft function were observed throughout the treatment period.

Keywords Embryonal · Rhabdomyosarcoma · Liver transplantation

Introduction

Pharmacological immunosuppression after solid-organ transplantation is thought to be responsible for an increased incidence of de novo malignancies. The evolution of such neoplasms is often faster than in non-transplanted patients, unless a drastic reduction of drug dosage is pursued [2]. Rhabdomyosarcoma is a tumor originating from striated muscle, accounting for 4–8% of malignancies in subjects less than 15 years of age. To date, no clear correlation has been reported between this neoplasm and drug-induced immunosuppression. The role of genetic factors in its pathogenesis has recently been pointed out, and although most cases are sporadic, the presence of associated abnormalities and familial syndromes has been described [1]. In spite of the aggressive behavior of these tumors, their sensitivity to chemotherapy (CHT) and radiation therapy (RT)

usually gives extensive possibilities for a multi-modal therapeutic approach. We report a case of embryonal rhabdomyosarcoma of the orbit that occurred 16 months after liver transplantation and was successfully treated with RT and CHT, which allowed stabilization of tumor growth for up to 38 months from the initial diagnosis.

Case report

A 21-year-old woman was hospitalized at our Department because of fulminant HBV-related hepatitis that was causing rapid deterioration of liver function. When she was admitted, cerebral computed tomography showed mild cerebral edema. Orthotopic liver transplantation was performed, a graft being used from a 70-year-old woman who had died from an intracranial hemorrhage, with no detectable infections or neoplastic diseases. During graft revascularization, 1,000 mg methylprednisolone were administered. Due to severe renal insufficiency, immunosuppression was started with anti-lymphocyte monoclonal antibodies (OKT3, 5 mg/day).

Primary graft non-function led to re-transplantation on postoperative day (POD) 3. The graft was procured from a 24-year-old man who had died from cranial trauma. No donor-related risk factors were recorded. A further 1,000 mg of methylprednisolone was infused during re-vascularization. Immunosuppression was switched to oral cyclosporine (13 mg/kg per day), steroids (200 mg on POD 1 tapered to 25 mg on POD 6), and azathioprine (100 mg/day). Steroid-resistant rejection required a second 10-day course of OKT3, with subsequent reinstatement of the cyclosporine-based regimen. Severe thrombocytopenia caused by anti-platelet antibodies was treated with methylprednisolone (60 mg/day) for 14 days, whereas azathioprine was discontinued. The patient was discharged on POD 66. Corticosteroid dose was progressively reduced and stopped by the 11th postoperative month, while the cyclosporine blood level was lowered to 130 ng/ml.

Sixteen months after transplantation, the patient developed diplopia and proptosis affecting the right eye. Cranial magnetic resonance detected a 2.5-cm retro-bulbar mass, occupying the entire medial wall of the orbit, with displacement of the optic nerve. The mass was initially presumed to be a hemangioma (Fig. 1). Due to its extension and the risk of damage to nerve structures, the tumor was only partially removed. Histological examination revealed an embryonal rhabdomyosarcoma, which contained tumor cells characterized by a high proliferation index (MIB 1-Ki 67 = 80%), with immunoreactivity for desmin (muscle-tissue specific—Fig. 2) and for polyclonal antibodies against striated muscle. The tumor was classified as T1a according to the TNM system [6] (absence of local invasion, metastatic lymph nodes, or distant metastases). Clinical and pathological staging classified the lesion as belonging to group III, according to the Intergroup Rhabdomyosarcoma Study (IRS) criteria [8].

Since the patient refused radical removal of the mass, which would have included complete emptying of the orbit, conventional RT (5,000 cGy in 5 weeks) was administered, but at the end of the treatment no signs of tumor regression were noted. Therefore, the patient received three courses of CHT over 3 months, according to the vincristine, D-actinomycin, and cyclophosphamide (VAC) scheme [4, 8], at 75% of the theoretical dose, except for vincristine, which was given at 100% of the full dose. Meanwhile, the cyclosporine blood level was lowered to 80–100 ng/ml, with frequent dose adjustments due to variations induced by chemotherapeutic agents. Because only slight shrinkage of the tumor was obtained, three further CHT courses were given with the same regimen, with full doses from the beginning.

No relapse of ocular symptoms was recorded, and liver function remained normal throughout CHT administration. There was no evidence of hepatitis recurrence, while mild side effects (asthenia, nausea, and leukopenia) were easily controlled with common antiemetic drugs and granulokines. There was no need for a drastic reduction or discontinuation of cyclosporine. Repeated cranial magnetic resonance imaging showed no tumor progression (Fig. 3), with persistent dislocation of the optic nerve and infiltration of the orbital muscles. No invasion of the nerve tissue was detected, and complementary investigations (total body computed tomography, bone scan) excluded extra-orbital metastases. Thirty-eight months after the initial diagnosis the patient is in good general condition, and leading a normal life.

Discussion

Rhabdomyosarcoma is an aggressive malignancy originating from striated muscle tissue and represents more

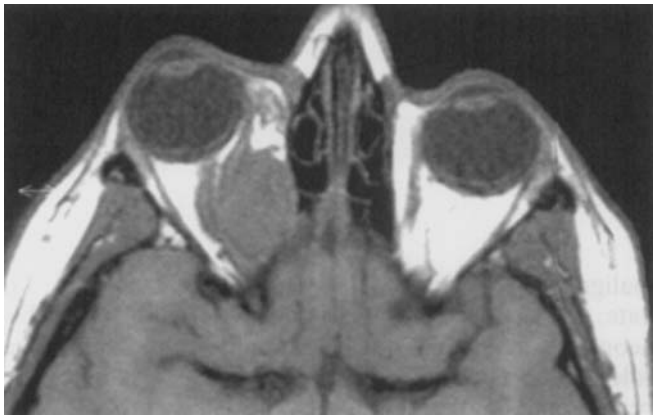

Fig. 1 Cranial magnetic resonance. In a T1-weighed scan an ovoid, hypointense mass (largest diameter: 2.5 cm) is visible inside the right orbit, not clearly dissociated from the medial rectus muscle and displacing the optic nerve towards the right

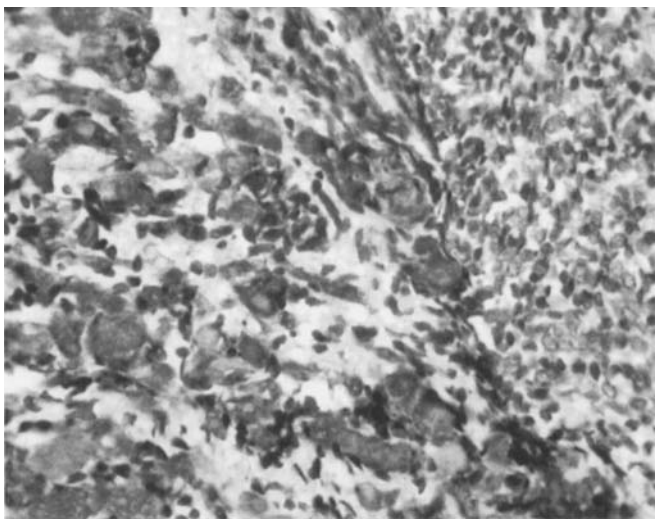

Fig. 2 Embryonal rhabdomyosarcoma immunostaining with desmin (40×). *On the left:* rhabdomyoblasts with typical brown cytoplasm pigments; *on the right:* small round immature cells, characterized by blue nuclei

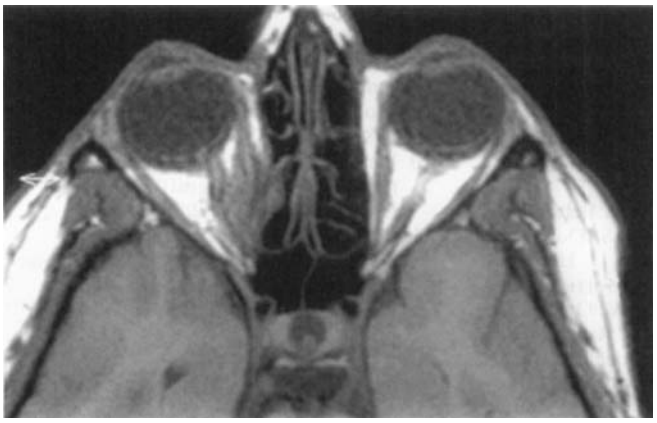

Fig. 3 Cranial magnetic resonance. After chemotherapy courses the tumor is still present, reduced in volume, without signs of local invasion (T1-weighed scan)

than half of the soft-tissue sarcomas found in children, while occurrence in adults is unusual [4, 8]. Genetic alterations might play a role in its pathogenesis [9]. Embryonal subtype and localization at the orbit generally carry a good prognosis, while adult age and advanced tumor stage are negative prognostic factors [3, 4, 7, 8]. Surgical removal is the treatment of choice, whereas RT and CHT are considered secondary approaches, although they are widely utilized in combination with surgery on the basis of the high sensitivity of such malignancies [4, 8]. The IRS classification identifies four clinical groups; patients belonging to group III have gross neoplastic residuals, but no extra-cranial spread after removal of the tumor [4, 8]. The standard treatment after incomplete surgical excision of rhabdomyosarcomas located in the orbit or head and of favorable histology is CHT with the VAC scheme or with the vincristine, cyclophosphamide, and doxorubicin (VAD-RC) scheme, associated with RT. With the current schedules, 5-year progression-free survival and patient survival are 85% and 90%, respectively [4, 8].

To our knowledge, there are no reported cases of embryonal rhabdomyosarcoma after liver transplantation. A case of cardiac rhabdomyosarcoma that occurred 14 years after kidney transplantation has been described, although diagnosis could be made only after autopsy [11]. A specific relationship with immunosuppression, namely, when pharmacologically induced, is far from being defined. This is the peculiarity of the present case, where a tumor rare in adults and not typical in transplant patients appeared several months after operation in an over-treated patient. Indeed, it is presumable that powerful immunosuppression could have accelerated tumor progression on a substrate of genetic alterations. On the other hand, immunosuppression and, especially, the use of OKT3, correlate with a high incidence of various types of de novo malignancies [10].

In spite of the incompleteness of surgical removal and the ineffectiveness of RT, appropriate CHT achieved stabilization of the disease, while histological subtype and site of occurrence allowed a good prognosis to be predicted. Moreover, the patient's young age increased her tolerance to therapy. In order not to overload immunosuppression or to damage an otherwise well-preserved liver function, we started CHT with sub-maximal doses. The cyclosporine blood level was kept between 80 and 100 ng/ml, which avoided the need for a drastic decrease in dosage, which represents the usual strategy with de novo malignancies [2]. However, we did not observe any increased tumor invasiveness or graft dysfunction. Full-dose CHT was administered only in the second phase, without severe side effects. When further therapies are planned, discontinuation of cyclophosphamide could also be considered, which would eliminate a potential source of treatment toxicity [4]. Moreover, in the case of tumor expansion, the possibility of switching immunosuppression from cyclosporine to rapamycin could be taken into consideration, based on the recent demonstration that this new drug was able to inhibit metastatic tumor growth and angiogenesis, with simultaneous effective immunosuppression, in an in vivo experimental model [5].

The occurrence of an embryonal rhabdomyosarcoma in a liver transplant recipient represented a unique case. Nevertheless, in spite of incomplete excision and relatively advanced age being the only negative prognostic factors, favorable histological subtype and site, and good compliance with a well-defined treatment scheme offer the patient a concrete chance of long-term survival.

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