

Case Report

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Brain Tumor as a Late Outcome of a Child with Nephrotic Syndrome - Is There Any Association with Immunosuppression?

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Introduction

Although it is clear that idiopathic nephrotic syndrome is associated with lymphoma, colon carcinoma, or bronchogenic carcinoma, malignant gliomas are uncommon among patients with idiopathic nephrotic syndrome.

Various immunosuppressives have been proposed for steroid dependent or resistant nephrotic syndrome. The risk of solid tumors and lymphoproliferative disorders is higher in post-transplantation patients. Using multiple immunosuppressive medications and some viral infections predispose the patients to malignancies. Moreover, intracranial diffuse large B-cell lymphomas have been reported in systemic lupus erythematosus patients receiving MMF [1,2].

The association of idiopathic nephrotic syndrome with some malignancies has been reported. We hereunder report a child with focal segmental sclerosis who presented with brain tumor eleven years after renal presentation. A 16- year-old boy presented with nephrotic syndrome since was 5 years old. He was a steroid responder at first but became steroid dependent after subsequent relapses. He received cyclosporine for two years and then mycophenolate mofetil was added for three years. After that, he received losartan and enalapril. Four years later, he developed glioblastoma multiforme. He passed away two years after surgical resection and chemo-radiotherapy.

Conclusion: The occurrence of brain tumor after immunosuppressive therapy in this child might be a late sequel or a coincidence. This might be an alarm for using immunosuppressive agents more cautiously.

Keywords: Glioblastoma; Immunosuppression; Mycophenolate Mofetil; Cyclosporine; Losartan; Enalapril; Nephrotic Syndrome.

Running Title: A case of Nephrotic Syndrome with Brain Tumor

Herein, we report the clinical course of a teenage boy with steroid-dependent nephrotic syndrome who developed a brain tumor four years after the cessation of immunosuppressive medication. He was treated with a combination of surgical resection and chemoradiotherapy. He passed away two years after therapy.

Case Report

A 16-year-old boy presented with nephrotic syndrome since the age of five. His renal biopsy showed focal segmental glomerulosclerosis. Initially, he was steroid responder but he became steroid dependent following subsequent relapses. Two years after presentation, cyclosporine was started at a dose of 4 mg/kg /day and his hypertension was controlled with enalapril,

losartan, and atenolol. After one year, he developed massive proteinuria (6gr/day); therefore, mycophenolate mofetil (1000mg/m²/day) was added to steroid and cyclosporine. Cyclosporine was tapered and stopped one year later. Full dose MMF was continued for 2 years and was then tapered during the following year. Proteinuria gradually decreased to 1.6 gr /day while GFR was within the normal range (100ml/min/1.73m²). Afterwards, enalapril and losartan were continued for one more year when they were discontinued by the patient. Forty months later, he was visited for a recent-onset sense of electric shock on his right hand and numbness and weakness on the right arm. On physical examination, the patient had a cushingoid appearance with moon facies. He appeared ill but not acutely toxic. His temperature was 38.5°C, blood pressure was 137/97 mmHg, pulse rate was 140/min, and respiration rate was 20/min. Neurologic examination revealed central facial palsy and decreased muscular force in the right upper extremity and inability to grasp with the right hand. Deep tendon reflexes were 2+ and symmetric. Fundoscopic examination was normal and so was the rest of the physical examination. His body weight was 102 kg and his height was 140 cm. Laboratory test results were as follows: hemoglobin: 10.8 g/dL, WBC: 5.3 × 10⁹/L, and platelets: 258 × 10⁹/L. blood urea nitrogen and serum creatinine were 12 mg/dl and 0.9 mg/dl, respectively. He had 24-h proteinuria range of 460 mg/day. Liver function tests were normal. Serum lipid profile revealed elevated total cholesterol and triglyceride levels (286 mg/dl and 217 mg/dl, respectively). Brain computed tomography scan showed a large mass (Figure 1). The mass was completely removed surgically and pathology examination was compatible with glioblastoma multiforme (Figure 2). Standard chemotherapy with vincristine, levostin, and dexamethasone was started and radiotherapy was administered for 33 sessions thereafter. The patient died few months later due to the relapse of the tumor which was unresponsive to therapy.

Discussion

Given the patient's past medical history of immunosuppressive medications, we reckoned a link between the previous use of medications and the brain tumor in this patient. It should be noted, however, that the two entities may only be a coincidence. The association of focal

segmental glomerulosclerosis with leukemia, rhabdomyosarcoma, [3], Wilm's tumor [4-5], invasive thymoma, [6], and non-Hodgkin's lymphoma [7] has been already reported. In all the above-mentioned cases, the presentation of FSGS is closely associated with tumor presentation. The difference of the presented case was the development of the brain tumor eleven years after renal manifestations and four years after the cessation of immunosuppressive medication.

However, since these medications suppress the immune system whose main function is to defend the body against infections and to prevent the development and progression of cancer, patients receiving immunosuppressive therapy are at increased susceptibility for infections and certain cancers. The exact mechanisms by which immunosuppressive medications promote tumor growth are not clearly defined and are still being investigated. Theoretically, several mechanisms are believed to be involved [8]. First, these medications may be directly oncogenic. Second, the compounds of these medications may potentiate the oncogenic effects of several environmental carcinogens. Third, these agents may cause the surveillance dysfunction of the lymphoreticular system which normally eliminates potentially malignant mutant cells. Fourth, the weakened host defenses may allow particular oncogenic viruses such as Epstein Barr virus and herpes simplex virus to become established and create malignant tumors. Furthermore, a growing body of evidence suggests the duration, intensity, and type of the immunosuppressant may be related to the development of certain cancers in the patients receiving immunosuppression. Cyclosporin A, an immunosuppressive therapy for steroid dependent or resistant nephrotic syndrome, induces growth arrest and apoptosis in experimental rats and human glioblastoma. It down-regulate the mTOR signaling pathway and P13k/Akt that interfere with the pro-invasive activity of microglia. Therefore, cyclosporine can hardly be considered as a predisposing factor for the late occurrence of glioblastoma multiforme in our patients [9].

There are several reports of the occurrence of central nervous system lymphoma in association with mycophenolate mofetil prescription in myasthenia gravis and systemic lupus erythematosus. In vitro studies show that the adhesion capacity of the tumor cells increase by mycophenolate mofetil. Blaheta et al. assessed

the effect of MMF on homophilic-binding neural cell adhesion molecule (NCAM) receptor and its role in neuroblastoma cell attachment to an endothelial cell monolayer [10]. They showed that MMF increased the number of adherent neuroblastoma cells by decreasing NCAM receptor expression. The authors concluded that MMF-based immunosuppressive regimen was associated with enhanced tumor cell invasiveness and thereby might increase the risk of tumor metastasis in tumors using hemophilic adhesion proteins for cell-binding. In contrast, Robson et al. longitudinally evaluated 13502 transplanted patients for three years and divided the patients to MMF and non-MMF users. They found a lower trend of developing lymphoma or other malignancies with MMF [11]. The same result was reported by O'neil et al. in another large cohort of patients with orthotopic heart transplantation [12]. Schrem et al evaluated the incidence of de novo malignancies after liver transplantation. They found a higher rate of malignancies in transplanted patients when compared to the general population. Overall, the malignancies were more invasive and had higher stages [13]. Furthermore, there are some reports about the increased rate of solid tumors after telmisartan. A systematic review was conducted by Rao et al. to evaluate the risk of lung cancer and other solid tumors in the new users of ARBs. The analysis revealed the risk of lung cancer was lower in those treated with ARBs compared to those who did not receive this medication [14]. The case presented here was a 16-year-old boy with glioblastoma multiforme which came to medical attention with new-onset neurologic symptoms. His past history included a steroid-resistant type of focal segmental glomerulosclerosis which made physicians to administer immunosuppression with MMF for 3 years that was withdrawn nearly 3 years ago. To describe the probable etiology of brain tumor in a young man, we assumed a link between the patient's previous immunosuppression and the brain tumor. However, to the best of our knowledge, no cases of glioblastoma multiforme have been reported in patients with nephrotic syndrome. Moreover, the possibility of the occurrence of glioblastoma multiforme in a young man irrespective of immunosuppression is not sufficiently low to be ignored and, therefore, it might be possible that the two entities are merely a coincidence. However, we found it worth noting to pay more attention to the possibility of such a relationship between the MMF use and the

development of glioblastoma multiforme although this report cannot establish causality. In addition, it is not currently possible to clearly determine whether the development of brain tumor in this patient who received MMF was merely due to chronic immunosuppressive therapy or was a reflection of the direct oncogenic effects of the medication. Whether or not MMF, cyclosporine, or ARB treatment may increase the risk of de novo malignancies has yet to be determined in prospective trials. As a result, further long-term cohort and registry studies are suggested to investigate whether this potentially serious association exists between the use of immunosuppressive agents and the development of cancer in non transplanted patients. Furthermore, given the increasing numbers of malignancies reported to be linked to immunosuppression therapies, it might be an alarm for using immunosuppressants more cautiously. The authors suggest that patients who have received long-term immunosuppressive therapy should be closely monitored for any change in their physical condition for even several years after the cessation of the immunosuppression therapy, particularly for acute changes that could be caused by an underlying malignancy.

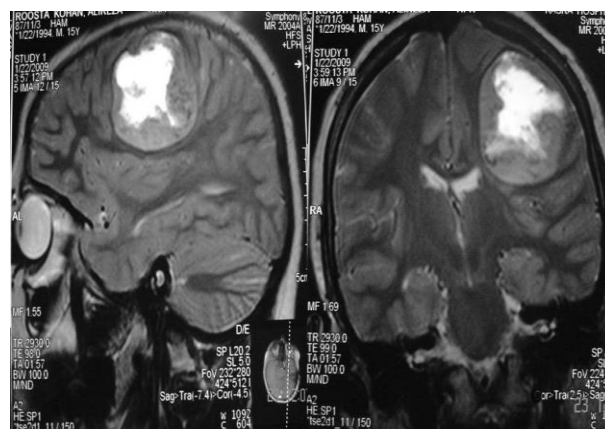


Figure 1. T2-weighted magnetic resonance image demonstrates an enlarged tumor of the right parietal lobe.

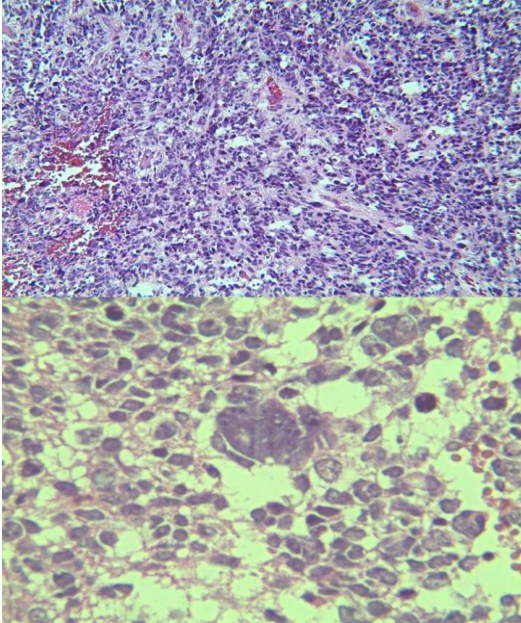


Figure 2. The picture shows astrocytic tumor with high cellularity and marked hyperchromasia, pleomorphism with brisk mitotic activity in favor of astrocytoma WHO grade IV or glioblastoma multiforme. The tumor is highly vascular. There is a small focus of necrosis in right lower part of the picture. (H&E, X400)

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Conflict of Interest

None declared

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