American Journal of Clinical Case Reports

ISSN: 2766-5844

Case Report

Toxoplasmosis of the Central Nervous System in the Late Period after Transplantation

Barbara Piekarska[1], Anna Zawiasa-Bryszewska[1], Anetta Barczak[2], Magdalena Pawlak[1], Anna Piekarska[2] and Ilona Kurnatowska[1]*

[1]*Department of Internal Medicine and Transplant Nephrology, Medical University of Łódź, Poland*

[2]*Department of Infectious Diseases and Hepatology, Medical University of Lodz, Poland*

Abstract

Background: Cerebral toxoplasmosis is extremely rare in Kidney transplant (KTx) recipients. In most reported cases, infection is activated in the early post-operative period, probably due to high doses of immunosuppressive drugs and it is usually associated with a high risk of mortality.

Case report: We present a unique case of cerebral toxoplasmosis developed 8 years after KTx. The serological markers indicated reactivation of an old infection. Antiprotozoal treatment including chronic maintenance doses was started. Additionally, due to Toxoplasma gondii and accompanying other viral and bacterial infections, the immunosuppressive treatment was minimized. Now, after 2 years of follow-up, the patient is alive with poor, but stable graft function.

Conclusion: There is lack of toxoplasmosis treatment recommendations for kidney transplant recipients, therefore we used our own treatment regimen, assuming that it would last until the immunosuppressive treatment was necessary.

Keywords: Kidney transplantation; Cerebral toxoplasmosis; Anti protozoal treatment

Introduction

Kidney transplantation (KTx) is the best treatment option for patients with End-Stage Renal Disease (ESRD). Although significant improvement in surgical techniques as well as induction and maintenance immunosuppressive regimens have increased allograft outcomes, infections still remain a leading cause of complications in kidney recipients [1]. The etiology of infections depends on the time elapsed after the procedure. Most infections in the first month after KTx are typically health care-associated infections, whereas late infections are similar to those in general population. Opportunistic infections like *Cytomegalovirus* (CMV), *Ebstein-Barr Virus* (EBV), *Pneumocystis jirovecii*, *Mycobacterium tuberculosis* and fungi most frequently present within the first 12 months after transplantation and can be modulated on the prior exposures and use of prophylaxis [1-3]. Transplant patients as compared to non-immuno compromised patients are also at higher risk of metabolic complications and of development of neoplasms, which can adversely affect post-transplant graft and recipients' outcomes [4].

Toxoplasmosis is extremely rare in KTx recipients. In the literature there are reported only a few cases [5-7]. Consequently, the frequency of cerebral toxoplasmosis in such patients has not been established. In majority of them the infection occurred in the early postoperative period most likely due to higher doses of immunosuppressive regimen [6].

In this report we present a case of cerebral toxoplasmosis developed 8 years after the KTx.

Case Presentation

A 61-year-old female farmer with ESRD of unknown cause had been hemodialyzed for two years before allogenic KTx from a deceased donor in 2014. Initially, she was treated with standard triple-drug immunosuppressive therapy consisting of tacrolimus (TAC), mycophenolate mofetil (MMF) and prednisone in doses adequate to a given period after KTx. Additionally; she was treated for arterial hypertension, depression and post-transplant diabetes mellitus (PTDM). The first four years after KTx were uncomplicated with good and stable graft function (eGFR 45 ml/min/1 to 60 ml/min/1.73 m^2). In March 2018 she was admitted to the Nephrology Department due to proteinuria accompanied by poor blood pressure control. Graft biopsy revealed thrombotic microangiopathy and there was suspicion of calcineur in inhibitor toxicity, thus the dose of TAC was minimized to achieve low trough level (TAC C0 3 ng/ml to 4 ng/ml) and MMF was increased from 1000 mg to 2000 mg a day with stable prednisone dose 5 mg/d. During the next 4 years her general condition was very good with good and stable graft function (eGFR 45-60 ml/min/1.73 m^2).

In September 2022 the patient was admitted to the Neurological Department at her place of residence after an episode of epileptic seizure followed by loss of consciousness. Her family reported that she had been illogical and aggressive for the past few weeks, and she expressed delusional thoughts accompanied by imbalance problems and blurred vision. The computer tomography (CT) of the head revealed a well-defined lesion in the left frontal lobe (Figure 1). An initial diagnosis of a tumor in the central nervous system (CNS) of unknown or uncertain nature was established and the patient was

Citation: Piekarska B, Zawiasa-Bryszewska A, Barczak A, Pawlak M, Piekarska A, Kurnatowska I. Toxoplasmosis of the Central Nervous System in the Late Period after Transplantation. Am J Clin Case Rep. 2024;5(1):1087.

Copyright: © 2024 Barbara Piekarska

Publisher Name: Medtext Publications LLC

Manuscript compiled: Jun 03rd, 2024

***Corresponding author:** Anna Zawiasa-Bryszewska, Department of Internal Medicine and Transplant Nephrology, Chair of Pulmonology, Rheumatology and Clinical Immunology, Medical University of Łódź, Department of Internal Diseases and Transplant Nephrology, Kopcińskiego22, PL90-153 Łódź, Poland

© 2024 - Medtext Publications. All Rights Reserved.

referred to the Neurosurgery Department.

The patient was in full verbal and logical contact upon admission to the Neurosurgery Department, and the initial neurological examination revealed no neurological deficits or focal symptoms. She was qualified for surgical treatment and the lesion was completely removed. A control CT revealed solely signs of typical edema in the operated area (Figure 2).

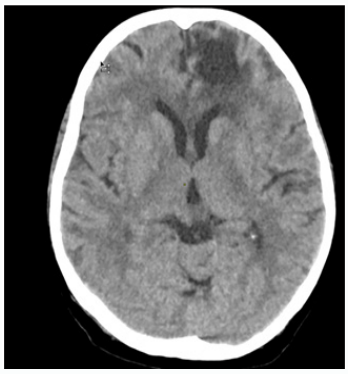

Figure 1: Well-defined lesion surrounded by the oedema in the left frontal lobe in the initial CT.

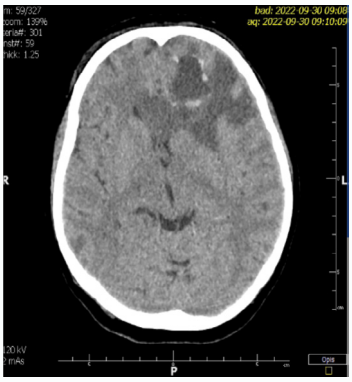

Figure 2: CT scan two days after left frontal craniotomy. Presence of hypodense lesion with the signs of typical oedema in the operated area and compression of the ventricular system.

After a few days the patient was discharged home in good general condition, without any neurological paresis, with prophylactic anticonvulsant treatment based on levetiracetam.

The histopathological examination showed that the lesion was probably caused by *Toxoplasma gondii*, and the patient was admitted to the Department of Infectious Diseases, where the presence of anti-toxoplasma IgG antibodies (>400 IU/ml; normal range: 0-7.2 IU/ml) with prominent level of avidity (index=0.556) and negative IgM antibodies was revealed in serum. To confirm the histopathological results and to find whether the infection was still present despite the removal of the toxoplasmic abscess, cerebrospinal fluid (CSF) was collected for PCR (Polymerase Chain Reaction) examination to determine the genetic material of *Toxoplasma gondii*. CSF was slightly turbid and flowed under increased pressure. The protein level and cell count in CSF fluid were mildly increased (respectively: 63.0 mg/dl and 53 cells/µl) and glucose level was normal (65 mg/dl). During the hospitalization in the Department of Infectious Diseases she suffered epileptic seizures which manifested in behavioral changes and periodic disturbances in the consciousness. Control CT revealed severe cerebral oedema. The anti-edema treatment with 20% mannitol and a switch of prednisone to dexamethasone 8 mg/d was implemented, the doses of MMF were reduced to 1000 mg/d, and TAC were kept low to maintain blood levels near the lowest recommended level. She was also treated with trimethoprim+sulfamethoxazole at 480 mg twice daily, as a part of empirical antiprotozoal treatment. Unfortunately, a control head MRI revealed recurrence of brain abscess (Figure 3), surrounded by oedema compressing the ventricular system. At the same time, positive PCR test for the presence of *Toxoplasma gondii* in CSF was obtained. Therefore, the diagnosis of *Toxoplasma gondii* infection with involvement of the CNS was confirmed. Consequently, the patient began treatment with pyrimethamine (starting with 200 mg on the first day, and continuing 50 mg on the following days), as well as supplementation with folinic acid at a dose of 15 mg daily. The pyrimethamine treatment improved the patient's overall condition and resolved the behavioral disorders. The dexamethasone doses were gradually reduced and were converted to prednisone in maintenance doses of 5 mg/d.

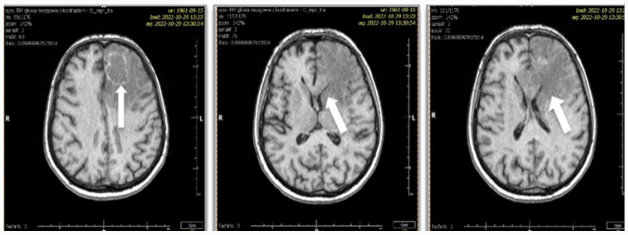

Figure 3: MRI scans one month after surgery. Recurrence of toxoplasmic brain abscess surrounded by oedema compressing the ventricular system (white arrows).

Furthermore, also a history of hepatitis B virus (HBV) infection was also discovered with positive serum test for total anti-Hbc and anti-HBs antibodies (109 IU/ml, positive when >10 IU/ml) with no signs of liver damage (ALT 12 U/l, normal range: 0-31 U/l). The decision of starting prophylaxis for reactivation of HBV infection with entecavir was postponed. Simultaneously, the diagnosis of human papillomavirus (HPV) wart-like skin lesions on the right hand was established (Figure 4). The presence of HIV infection was excluded.

Figure 4: Human PapillomaVirus (HPV) wart-like skin lesions on the right hand.

In November 2022, the patient was admitted to the Nephrology Department due to diabetes mellitus decompensation (glycemia values ranging from 700 mg/dL to 946 mg/dL). She also developed

© 2024 - Medtext Publications. All Rights Reserved.

oral and genital mycosis and cold sores caused by *Herpes Simplex* Virus (HSV). Moreover, urinary infection caused by *Escherichia coli* and *Klebsiella pneumoniae* was diagnosed. Treatment with insulin was implemented. In addition, due to fungal, bacterial and HSV infection, fluconazole, acyclovir and meropenem were introduced in doses appropriate to graft function. Additionally, cytomegalovirus infection was detected and the treatment with valganciclovir was conducted until two consecutive negative CMV-DNA tests. The MMF was finally stopped due to multiple infections and the immunosuppressive regimen consisted only of TAC and prednisone.

The control head CT scan made after one month of antiprotozoal treatment revealed a significant reduction of edema in the area of the left frontal lobe and disappearance of the new abscess (Figure 5). Currently after a 24-month follow-up, the patient is in quite good general condition, still non-dialyzed, with poor, but stable graft function (eGFR around 15 ml/min/1.73 m^2), treated with low doses of immunosuppressive drugs and maintenance antiprotozoal regimen with pyrimethamine and folinic acid (it seems that it should be continued for life in immunosuppressive patients). The results of laboratory tests from the particular time points of post trans plant care are presented in Table 1.

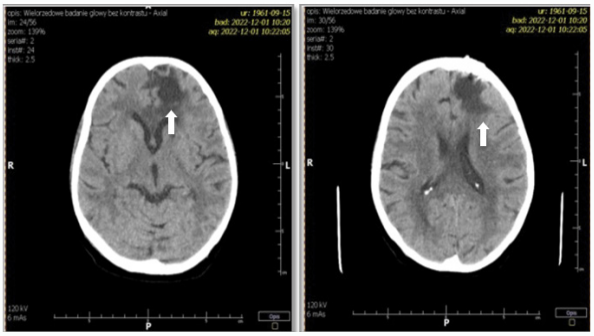

Figure 5: CT scans after one month of treatment. Significant reduction of edema in the area of the left frontal lobe and disappearance of the new toxoplasmic abscess (white arrow).

Discussion

We present a rare case of cerebral toxoplasmosis diagnosed 8 years after KTx. Such a late onset is extremely rare in post-transplant patients, because most cases of such toxoplasmosis occur within 3 months after the transplantation, probably due to the higher doses of immunosuppressive treatment used in this period. Cerebral manifestation of toxoplasmosis is usually seen in HIV infected patients [8], but our patient was HIV negative. To our knowledge there are less than seventy such cases described in medical literature [5-7]. The rareness of this clinical phenomenon leads to difficulties in diagnosis and uncertainty with regard to proper antiprotozoal treatment [9].

Because of the high level of IgG anti-toxoplasma antibodies with the high level of avidity and low level of IgM antibodies we can suspect reactivation of a previously existing infection in our recipient. We can speculate that the probable time of reactivation of toxoplasmosis took place after the use of high doses of MMF after thrombotic microangiopathy complications. There are few reported cases of cerebral toxoplasmosis that link the disease with the use of high doses of MMF [10-12] and more research is needed to confirm this relationship.

In chronic infections, like in this case, the first step should be decreasing the force of immunosuppression. Considering high doses of MMF, which suppress the activity of B and T lymphocytes and inhibit antibodies production, we finally decided to withdraw MMF and to continue immunosuppressive therapy as a double-drug treatment, consisting of prednisone and TAC adjusted so as to keep low concentration in the range of TAC C0: 3 ng/ml to 4 ng/ml.

Testing patients for the presence of anti-toxoplasma antibodies before any type of organs transplantation should be considered. Knowledge of patients' serological status would allow avoiding such complications in the post-transplantation period. During differential diagnosis it is crucial to take into account the patient's environment and possible contact with raw meat or animal feces. Living in a rural environment, working in a slaughterhouse, or having cats increase the risk of developing toxoplasmosis [13]. Conservative treatment is the treatment of choice in cerebral toxoplasmosis because it makes lesions disappear completely without leaving neurological deficits, whereas surgical treatment does not result in full recovery and may often lead to permanent neurological consequences, thus it is not recommended. It is well demonstrated in our case: despite the complete removal of the first brain abscess, another formed within a month.

Toxoplasmosis treatment recommendations for kidney transplant recipients have not been established due to little clinical experience in this field. In several cases toxoplasmosis was treated for 2 or 3 months with success [5]. However, lack of long-term follow-ups leads to the question: will this standard treatment be enough for patients' recovery and will it prevent reactivation of the infection? Or, if the necessity to maintain immunosuppressive therapy in transplant recipients which in itself increases the risk of reactivation of toxoplasmosis, should indicate the necessity to implement secondary prevention regimen with antiprotozoal drugs in case the immuno suppressive treatment is continued for life, or until graft failure? Unfortunately, the influence of chronically used antiprotozoal treatment on the graft function is not known yet. There are no guidelines for drugs doses adjustments depending on the kidney function.

Another problem with antiprotozoal treatment is its still unknown interaction with TAC. TAC is a drug metabolized by cytochrome P450 (CYP3A5), which takes part in the metabolism of various drugs. Furthermore, TAC has a narrow therapeutic window [14]. Too low drug concentration may lead to graft rejection too high drug concentration may lead to nephro- and neurotoxicity, carcinogenesis, and infectious complications. While introducing any drugs, especially metabolized by the same enzyme system, there is a necessity of careful monitoring of TAC concentration and dose adjustment to keep TAC concentration in the therapeutic window.

Conclusion

We concluded that toxoplasmosis should be taken into consideration in differential diagnosis of focal lesions in the CNS in transplant recipients. The treatment of toxoplasmosis in a transplant patient is a real art it requires careful monitoring of the patient because there is no objective data on appropriate anti protozoal drug doses and on how long the treatment should be carried out.

References

1. Karuthu S, Blumberg EA. Common infections in kidney transplant recipients. Clin J Am Soc Nephrol. 2012;7(12):2058-70.
2. Agrawal A, Ison MG, Danziger-Isakov L. Long-Term Infectious Complications of Kidney Transplantation. Clin J Am Soc Nephrol. 2022;17(12):286-95.
3. Hellemans R, Abramowicz D. Cytomegalovirus after kidney transplantation in 2020:

© 2024 - Medtext Publications. All Rights Reserved.

Table 1: Laboratory results from particular time points of post transplant care.

	Nephrology Department-thrombotic microangiopathy complication	Neurosurgery Department before lesion removal	Department of Infectious Diseases - diagnosis of Toxoplasma gondii infection		Nephrology Department diabetes decompensation and numerous infectious complications		Follow-up data		
	05.04.18	**26.09.22**	**19.10.22**	**06.11.22**	**29.11.22**	**12.12.22**	**14.02.23**	**18.05.23**	**20.09.23**
Creatinine (mg/dl)	1.06	1.69	1.58	1.62	1.93	2.16	3.87	3.35	3.2
GFR (ml/min/173m²)	57	32	34.95	33.91	28	24	12	14	15
Urea (mg/dl)	5.6	98	74	103	.	.	160	96	155
Proteinuria (g/1)	0.89	.	0.5	-	0.35	-	0.47	0.16	0.16
Erythrocyturia (RBC/HPF) (Red blood cell per high power field)	01-Feb	-	0-3	.	0.2	0.1	0	.	.
ALT (Alanine aminotransferase) (U/I)	-	-	12	-	34	29	26	17	19
Bilirubin (mg/dl)	.	.	.	.	0.57	0.35	-	0.49	0.31
RBC (Red Blood Cells) (10^6/µl)	4.62	4.02	4.06	3.92	4.26	3.06	3.28	3.34	3,06
Hgb (Hemoglobin) **(g/dl)**	13.2	11.1	11.4	10.9	12.1	8.9	10.7	10.2	10
Hct (Hematocrit) (%)	39.5	34	34.6	32.7	34.8	26	32.2	31.5	30.2
WBC (white blood cells) (10^3/**µl**)	5.6	5.8	6.8	10.7	4.3	4.8	6.8	6.7	4.6
PLT (Platelets) **(10^3/µl)**	183	232	223	191	155	120	164	182	170
Eosinophils (10^3/µl)	0.1	0	0.1	0	0.01	0	0.02	0	0.04
Lymphocytes (10^3/µl)	2.1	0.4	0.6	0.5	0.4	0.6	0.7	0.6	0.6
CRP (C-reactive protein) (mg/l)	1.7	-	5.07	0.39	9.6	2.1	10.6	3.9	1.9
INR	1.19	1.1	1,29	1.17	.	.	.	-	.
Glycemia (mg/dl)	-		-	-	942	153	110	126	81

moving towards personalized prevention. Nephrol Dial Transplant. 2022;37(5):810-16.

4. Cohen E, Korah M, Callender G, Belfort de Aguiar R, Haakinson D. Metabolic Disorders with Kidney Transplant. Clin J Am Soc Nephrol. 2020;15(5):732-42.

5. Renoult E, Georges E, Biava MF, Hulin C, Frimat L, Frimat L, et al. Toxoplasmosis in kidney transplant recipients: report of six cases and review. Clin Infect Dis. 1997;24(4):625-34.

6. Da Cunha S, Ferreira E, Ramos I, Martins R, De Freitas L, Borges JL, et al. Cerebral toxoplasmosis after renal transplantation. Case report and review. Acta Med Port. 1994;7 Suppl 1:S61-6.

7. Wulf MW, van Crevel R, Portier R, Ter Meulen CG, Melchers WJ, van der Ven A, et al. Toxoplasmosis after renal transplantation: implications of a missed diagnosis. J Clin Microbiol. 2005;43(7):3544-7.

8. Dian S, Ganiem AR, Ekawardhani S. Cerebral toxoplasmosis in HIV-infected patients: a review. Pathog Glob Health. 2023;117(1):14-23.

9. Mukherjee A, Bal C, Tripathi M, Das CJ, Shamim SA. Cerebral Toxoplasmosis Masquerading Cns Lymphoma on FDG PET-CT in Post Renal Transplant Patient. Indian J Nucl Med. 2017;32(2):148-49.

10. Bernardo DR, Chahin N. Toxoplasmic encephalitis during mycophenolate mofetil immunotherapy of neuromuscular disease. Neurol Neuroimmunol Neuroinflamm. 2015;2(1):e63.

11. King R, Sekar P, Patel H, Naveed M, Aqtash S, Adroja S, et al. CNS toxoplasmosis, a rare presentation in a patient with Myasthenia Gravis. IDCases. 2023;32:e01780.

12. Pistacchi M, Gioulis M, Zirillo M, Francavilla E, Marsala SZ. Cerebral toxoplasmosis in undifferentiated connective disease treated with mycophenolate mofetil: an unusual case report. Acta Neurol Belg. 2016;116(4):633-36.

13. Robert-Gangneux F, Dardé ML. Epidemiology of and diagnostic strategies for toxoplasmosis. Clin Microbiol Rev. 2012;25(2):264-96.

14. Schutte-Nutgen K, Tholking G, Suwelack B, Reuter S. Tacrolimus - Pharmacokinetic Considerations for Clinicians. Curr Drug Metab. 2018;19(4):342-50.

© 2024 - Medtext Publications. All Rights Reserved.