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ACUTE BRAIN DAMAGE IN A 56-YEAR-OLD WOMAN WITH A 20-YEAR-OLD
TRANSPLANTED KIDNEY AS A COMPLICATED DIFFERENTIAL DIAGNOSTIC PROCESS – A
CASE REPORT

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Key words: transplantation, posttransplant lymphoproliferative disorder (PTLD), progressive multifocal leukoencephalopathy (PLM), acute brain damage

Abstract

Introduction: Acute central nervous system (CNS) damage in patient who had received organ transplant is an extremely difficult and complex clinical issue that spans a wide spectrum of differential diagnosis with ischemia, posttransplant lymphoproliferative disorders (PTLDs), infections, lymphomas, and progressive multifocal leukoencephalopathy (PML). PTLDs are a clinically and histopathologically heterogeneous group of diseases that most often occur in heavily immunocompromised population after solid organ transplantation (SOT), probably related with the infection or reactivation of Ebstein-Barr virus (EBV) infection, whereas PML is an infectious disease caused by JC virus (JCV).

Case description: A 56-year-old female, 20 years after renal transplantation from deceased donor, was admitted to the hospital as an emergency due to sensory aphasia and memory disorders. CT examination revealed a diffuse expansive process in the temporo-parieto-occipital and left frontal area. MRI results suggested changes associated with PML, however JCV was not found in cerebrospinal fluid. The disorders progressed quickly, both clinically and radiologically – the patient developed central facial palsy, paresis of limbs and positive Babinski sign on the left. Second radiological examination (CT) also suggested PML. Due to the rapid deterioration of the patient's general condition further diagnostic examinations (MR with contrast and brain stereotactic biopsy) could not be performed. After almost two months of the commencement of the diagnostic process the patient died. Autopsy revealed that the cause of death was acute central nervous system (CNS) damage in the course of monomorphic posttransplant lymphoproliferative disorder (CNS-PTLD).

Conclusions: Rapid deterioration of mental status can be the first symptom of CNS-PTLD in solid organ transplant population, that is a dangerous and life-threatening condition in immunocompromised patients.

Introduction

Acute CNS damage in patient who had received solid organ transplant (SOT) is an extremely difficult and complex clinical issue that spans a wide spectrum of differential diagnosis of ischemia, posttransplant lymphoproliferative disorders (PTLDs), infections, lymphomas, and progressive multifocal leukoencephalopathy (PML) [1]. PTLDs are a clinically and histopathologically heterogeneous group of lymphoid and/or plasmatic proliferations (from benign polyclonal lymphoid hyperplasia to monomorphic aggressive lymphomas) that most often occur after SOT, with uncommon primary central nervous system involvement. The pathogenesis of B-cell derived PTLD is mostly associated with Ebstein-Barr virus (EBV) infection, that mediate B cell proliferation in immunocompromised patients . Cytomegalovirus (CMV) and hepatitis C virus (HCV) may be also involved in pathogenesis of PTLD, however their role is not well established. PML is a demyelinating disease of the CNS that is caused by reactivation of the polyomavirus JC (JCV). Primary asymptomatic infection with JCV occurs in childhood. The virus remains latent in kidneys and lymphoid tissue, but, in terms of profound immunosuppression, it can reactivate, spread to the brain, and induce a lytic infection of oligodendrocytes, which produce myelin in CNS. As the name indicates, PML is a multifocal and progressive disease, which most often manifest with subacute neurological symptoms, such as ataxia, change of mental status, hemiparesis. The diagnosis of PTLDs or PML should be suspected in SOT recipients with mental status changes or new neurological findings. They are one of the most serious and potentially fatal complications after transplantation [2; 3].

Case description

A 56 - year old woman, who underwent kidney transplantation 20 years ago from deceased donor, currently treated with cyclosporine, mycophenolate sodium and prednisone, was urgently admitted to the Department of Nephrology and Transplantation Medicine due to worsening of general condition, new neurological findings, nausea and diarrhea. A month before the patient was hospitalized in the regional hospital on Neurological Department because of sudden appearance of memory disorders and speech abnormalities. In the brain tomography (CT) without contrast a nonspecific change with suggestive of

edema was described in the left temporal-parietal-occipital region, which was later described in the MRI as possibly caused by progressive multifocal leukoencephalopathy (PML). The examination of cerebrospinal fluid revealed cytosis and elevated level of protein, but the JC virus (JCV) was absent. In order to confirm the diagnosis, the stereotactic biopsy of the brain was planned. During the stay in the Department of Nephrology and Transplantation the patient's condition was stable at the beginning, with memory disorders as a dominant symptom. The immunosuppression was minimized, with only corticosteroid treatment maintained. Neurological and neurosurgical consultations took place, and the date of the brain stereotactic biopsy was arranged in order to confirm the diagnosis. At admission her kidney function was impaired (serum creatinine concentration at 2.93 mg/dL), hsCRP 10.94 mg/L, ESR 20 mm/h, procalcitonin 0.15 ng/mL (normal values < 0.1 ng/mL), and she was HBsAg-negative (but anti-HBc-positive), HCV-RNA positive, JVC-, BKV-, and VZV-negative. Unfortunately EBV was not done, however in brain autopsy EBV positivity was confirmed. The CT was performed and it showed progression of the hypodense lesions in the white matter of left brain hemisphere and smaller changes in right brain hemisphere. At the same time the patient was diagnosed with cytomegalovirus infection (CMV-DNA 16700 copies/mL), that was treated with intravenous Ganciclovir. Subsequently septicemia with *Staphylococcus aureus* MSS was established, treated with meropenem, according to antibiogram. The brain biopsy was delayed for the time of antiviral and antibiotic treatment, but was not performed because of patient's poor general condition. Because of decrease in urine output, increase of creatinine and urea serum level as well as hyperkaliemia the patient started hemodialysis treatment. Performed CT revealed brain edema and progression of previously described lesions which compressed the ventricles (Figure 1). Dexamethasone was introduced as antioedematous treatment. The patient's condition deteriorated steadily, and after three weeks the patient died. The autopsy was performed at the Department of Pathomorphology. Histopathological examination of the brain revealed monomorphic primary central nervous system posttransplant lymphoproliferative disorder (M-PCNS-PTLD) presenting itself as spreading destructive lymphocytic lesions in the structures of central nervous system built from atypic large B-cells, located mostly around vessels (angiocentric pattern), infiltrating the nervous tissue (Figure

2). Based on the histomorphological and immunohistochemical examination – positive EBV antigen, negative SV40 status – the diagnosis of PML was excluded. Wide destruction of the CNS in the course of posttransplant lymphoproliferative disease was established as a cause of death.

Discussion

Solid organ transplant (SOT) recipients are a special group of patients because of their immunocompromised status. Long lasting immunosuppressive treatment protects them from transplant rejection but at the same time exposes them to diseases that rarely occur or occur not at all in the general population. Posttransplant lymphoproliferative disorders (PTLDs) and progressive multifocal leukoencephalopathy (PML) are rare but potentially life-threatening complications of SOT. Mateen et al. described so far 69 cases of PML after transplant of various organs [4]. Taking into consideration overall number of performed transplants, the possibility of patient developing PML after renal transplant seems to be infinitesimal. PTLD also occur rarely in this group and intracranial localization is extremely rare [5]. Although, the number of PTLD's incidence by renal transplant recipients has been lately increased [6]. The pathogenesis of mostly PLTD is related to EBV-infected memory cells transforming into clonal population, with the highest risk in EBV seronegativity in the recipient at transplantation. As defined by World Health Organization (2001) PTLDs are lymphoid proliferations or lymphomas that develop in SOT or bone marrow recipients. They are considered as a spectrum of disease, from EBV-driven polyclonal proliferation to malignant lymphomas that can be EBV-positive or EBV-negative. The vast majority are of the B-cell phenotype, and rare are T-cell dependent (about 14%) or derive from NK-cells (about 1%) [7]. PTLDs occur in heart, lung and multiorgan transplants more frequent than in renal and liver transplant recipients due to higher immunosuppressive treatment. The dependence of diseases' appearance on specific immunosuppressive treatment is not clear, and some authors confirm it [8], whereas some deny these findings [9]. In case of both diseases (PTLD and PML) diagnostic algorithm is based on gadolinium-enhanced MRI of the head as well as cerebrospinal fluid analysis. To confirm PML the presence of JCV in

CSF must be shown, however negative result does not allow excluding this disease. The most specific method for verifying PML, when the gadolinium-enhanced MRI cannot be performed is brain biopsy.

Involvement of the CNS in PTLD is relatively uncommon, with incidence between 5% and 30% of cases, but CNS may be the only area involved (primary central nervous system-PTLD) [10]. The incidence in renal transplant recipients varies from 0.6% to 2.5% [2; 7]. PTLD range from early lymphoid proliferations to malignant lymphomas with 80-90% of causes being associated with EBV infection, with the highest incidence in the first posttransplant year, but the increase risk remains lifelong compared to the general population [10]. The diagnosis in our patient, as other patients with neurological symptoms, started with CT/MRI imaging, but complications that developed during hospitalization made it impossible to establish intravital diagnosis.

It is interesting that first symptoms appeared in 56-years old woman and 20 years post-transplant, compared to the mean of 4.4 years in the study of Cavaliere et al., but 23% (8 of 34) patients developed primary CNS-PTLD beyond 10 years after transplantation [12], and the average age at the onset of the disease is the third decade for immunocompromised and the fifth decade for immunocompetent patients [13]. It supports the bimodal incidence profile and differences in risk factors and clinical course [14]. Early-onset PTLDs occur during the first year, mainly in the graft, while late-onset PTLDs occur thereafter, with multiple localizations and poor prognosis. Michonneau et al. described 52 kidney transplant recipients with late-onset PTLD (aged 53.7 years in first cohort and 49.1 years in the second one), in whom two thirds received induction therapy before transplantation (57% between 1980 and 1999, and 80% between 2000 and 2010) and the median interval between transplantation and late-onset PTLD diagnosis was 97 (65-183) months in first cohort (1980-1999) and 115 (74-163) months in the second cohort (2000-2010), with male predominance for all cases (M/F = 1.47) [15]. Extranodal localization was found in about 85%, with CNS involvement in 11 patients (21%). In cases of CNS involvement sex ratio was different, with female predominance (M/F = 0.57) [15]. Moreover, plasma EBV- and PCR testing is often not useful in CNS involvement [16]. Despite treatment, firstly based on reduction of

immunosuppression (halving of calcineurin inhibitors and cessation of the second agent, usually mycophenolate) apart from corticosteroids, surgery, radiotherapy and chemotherapy (earlier CHOP: cyclophosphamide, hydroxydaunorubicin-doxorubicin, oncovin-vincristine, prednisone, nowadays rituximab (R) or R-CHOP), the prognosis of PCNS-PTLD is poor, with median survival only 13 weeks after diagnosis, but in some cases the survival is significantly longer [13].

Conclusion: Primary central nervous system – post-transplant lymphoproliferative disorder (PCNS-PTLD) may appear at first with altered mental status and memory disorders. It is important to take PCNS-PTLD into account as a diagnosis in immunocompromised patients after solid organ transplantation when in MRI contrast-enhancing lesions are observed.

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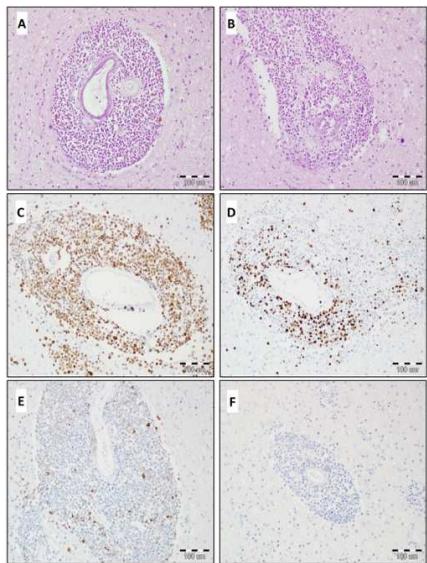
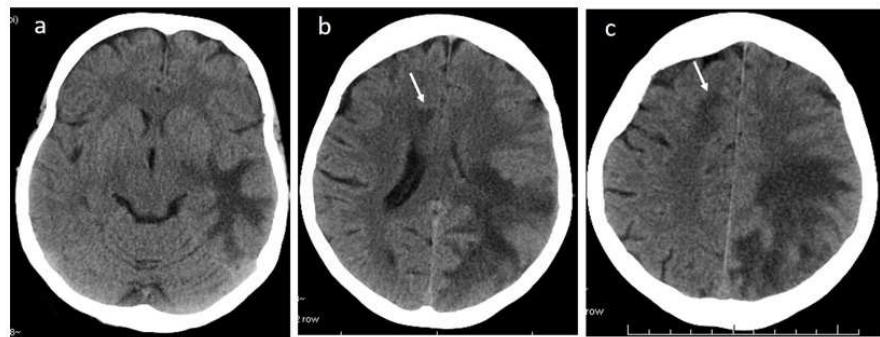


Figure 1. Monomorphic primary central nervous system posttransplant lymphoproliferative disorder (M-PCNS-PTLD) – extensive, destructive lymphocytic infiltrates within the CNS structures consist of atypical large B cells with typical angiocentric pattern (A, B; H&E staining, 200×). Immunohistochemical analysis of M-PCNS-PTLD. Predominance of CD20-positive B lymphocytes in neoplastic infiltration (C, 200×). Intermediate proliferation index measured by Ki-67 immunoexpression (30-35% of positive cells) (D, 200×). EBV(+) neoplastic cells in CNS infiltration (E, 200×) with lack of SV40 (BKV) reactivity (F, 200×).



Large hypodense area mainly within the white matter of the left temporal, occipital, parietal and partially also frontal lobes as well as a smaller area of the similar appearance in the right frontal lobe (arrows)

The findings are non-specific suggestive of vasogenic edema associated with neoplastic or inflammatory infiltration

Highlight

1. Solid organ transplant (SOT) recipients are at risk of serious CNS injury
2. Mental status disorders may be first symptoms of PML or PTLD in SOT recipients
3. Gdolinium enhanced MRI and brain biopsy are diagnostic methods for PML and PTLD
4. JC virus for PML and EB virus for PTLD should be evaluated in SOT recipients
5. CNS PTLD or PML can manifest as MRI contrast-enhancing lesions