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# Creutzfeldt - Jakob disease as a reason of neurological deterioration in the patient with acute lymphoblastic leukemia after allogeneic hematopoietic stem cell transplantation

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## Keywords

Creutzfeldt-Jakob disease; Neurological deterioration; Allogeneic hematopoietic stem cell transplantation; Differential diagnosis.

## Abbreviations

BS: Peripheral blood smear; CSF: Cerebrospinal Fluid; EEG: Electroencephalogram; MRI: Magnetic Resonance Imaging; FC: Flow Cytometry; PCR: Polymerase Chain Reaction; CR: Complete Remission; MRD: Minimal Residual Disease; ALL: Acute Lymphoblastic Leukemia; CMV: Cytomegalovirus; EBV: Epstein-Barr virus; HHV-6: Human Herpesvirus 6; JCV: human polyomavirus 2; ADV: Adenoviruses; HSV: Herpes Simplex Virus; VZV: Varicella-Zoster Virus; LA: Lupus Anticoagulant; RF: Rheumatoid Factor; Anti-MPO cANCA: Anti-Myeloperoxidase Anti-Neutrophil Cytoplasmic Antibodies; Anti-PR3 cANCA: Anti-Proteinase 3 Anti-Neutrophil Cytoplasmic Antibodies; Anti-TPO: Antithyroid Antibodies; ANA: Antinuclear Antibodies; DS DNA: Double-Stranded Deoxyribonucleic Acid.

## Description

Neurological pathology is considered rare but serious complications after allogeneic Hematopoietic Stem Cell Transplantation (allo HSCT). The presented case report shows it poses a diagnostic challenge for physicians and a great threat for patients.

A 64-year-old patient was admitted to the hospital due to progressive alteration of consciousness for three weeks. Sixty days prior, the patient had undergone an allo-HSCT due to high-risk Acute Lymphoblastic Leukemia (ALL) with initial infiltration of Cerebrospinal Fluid (CSF). At day 36th post allo HSCT, Complete Remission (CR) with 100% chimerism was confirmed. At day 45th post allo HSCT patient presented with

**Table 1:** Differential diagnosis.

| Test | Results | Differential diagnosis |
|---|---|---|
| Morphology | WBC ($10^3$/ul): at admission: 1,83; max. 8,21, Hgb (g/dl): at admission: 10,8, Plt ($10^3$/ul): 154<br>PBS: no blasts in blood smear | Relapse of ALL excluded |
| Bone marrow | CR; MRD negative | |
| Chimerism in bone marrow | 100% of allogeneic signal | |
| CSF | Normal pleocytosis, no ALL infiltration by flow cytometry | |
| Blood biochemistry (at admission) | creatinine (0,55-1,02 mg/dl): 0,64, norm never exceed; urea (11-43 mg/dl): 19; uric acid (2,6-6 mg/dl): 2,8, sodium (135 - 145 mmol/l): 128, norm never exceed,<br>TSH (0,35-4,94 uIU/ml): 0,6361, ft3 1,77-7,05 pmol/l): 2,35, ft4 (9,01-19,05 pmol/l): 13,19, ASPAT (5-34 U/l): 20, GGTP (9-36 U/l): 37, haptoglobin (0,3-2 g/l): 2,18, alkaline phosphatase (40-150 U/l): 46, Mg2+ (1,6-2,6 mg/dl): 1,62, albumin (3,2-4,6 g/dl): 3,7 | Central pontine myelinolysis (hyponatremia) was excluded, as the correction was performed with steady NaCl-infusion and no improvement was observed. An organ failure was excluded. |
| IgM (blood)<br>IgG (blood)<br>IgA (blood)<br>IgA (CSF) | IgA (blood) 2,2 g/l (0,85-4,5); IgG max. 19 g/l, min. 4,57 g/l, (8-17); IgM 0,538 g/l (0,6-3,7); IgA (CSF) 5,52 mg/l (0,5) | incorrect ratio of IgA concentration in blood and CSF suggests CJD |
| CRP<br>Procalcitonin | CRP (0,2-5 mg/l): at admission: <0,5, max.: 102,6, min.: <0,5, mediana: 3,7.<br>Procalcitonin (to 0,05 ng/ml): at admission: 0.02; max. 0,82 | Bacterial, fungal and parasite infection excluded |
| CSF | Normal pleocytosis; bacterial and fungal coulter: negative | |
| Aspergillus and candida antigens in blood and CSF – immunoenzymatic test ELISA | Negative | |
| Urine (dipstick test, microscopic exam and culture) | Negative | |
| Toxoplasma gondii blood serology | Negative | |
| CMV – PCR assessment of viral copies | CMV positive in blood – at admission 2044 copies/ml; decrease of copies titl 18.10.2021, when the result was 3195 copies/ml. Since then amount of copies was decreasing till negative result before the discharge; negative in CSF | CMV: no clinical improvement with decrease of the viral load |
| EBV, HHV-6, JCV, ADV, HSV 1 & 2, VZV, Parvovirus B19 | Negative | Other viral infections were excluded |
| Blood: LA, RF, Anti-MPO pANCA, cANCA, dsDNA, ANA, anti-cardiolipin, anti-TPO, anti-ß2-glycoprotein | Negative | No response to immunosuppressive therapy, antibodies in blood and in CSF were negative: limbic encephalitis excluded<br><br>As there was no improvement after immunotherapy Graft-versus-Host Disease was also ruled out |
| CSF: anti-AMPA (GluR1/GluR2), anti-GABA B, anti-NMDA, anti-DPPX, anti-CASPR 2, anti-LGl 1 (limbic encephalitis antibodies test) | Negative | |
| Cranial MRI | Hyperintensity in left caudate and left lentiform nuclei as well as the left parietal and temporal lobe in T2-weighted image, TIRM and DWI. MRI is not typical for ischemi and did not change during the follow-up. | Changes described in MRI were not suggestive of ischemia Limbic encephalitis and was excluded<br>After differential diagnosis, CJ disease was suggested |
| EEG | Slow basal activity of both cerebral hemispheres with generalized synchronic periodic sharp wave complexes and spikes within theta waves | Epilepsies was excluded and CJ disease was suggested |
| 14-3-3 protein in CSF | Positive | CJ disease |

fresh memory alterations. Reactivation of Cytomegalovirus (CMV) was diagnosed, and the patient started therapy with valganciclovir. Despite the decrease of the viral load of CMV, the neurological state of the patient continued to deteriorate, and the patient required hospital admission. At this time, she was disoriented, basic neurologic examination revealed overactive deep reflexes and a negative coherence test. The brain computer tomography ruled out acute ischemia. Bone marrow and CSF analysis excluded relapse of ALL. Viral (except for CMV reactivation), bacterial, fungal and parasite infection were ruled out. Hyponatremia, probably secondary to dehydration, was slowly corrected [1]. All potentially neurotoxic medication, e.g. cyclosporine, tacrolimus were changed or stopped. The patient fell into a coma, shortly afterwards. Horner syndrome and pyramidal-extrapyramidal symptoms were diagnosed. The brain magnetic resonance revealed hyper intensity in left caudate and left lentiform nuclei as well as the left parietal and temporal lobe in T2-weighted image, TIRM and DWI. With suspicion of limbic encephalitis, firstly treatment with plasmapheresis and corticosteroids, and secondly with immunoglobulins, mycophenolate mofetil and anti CD20 was administered with no improvement. Finally, negativity of the antibody tests of blood and CSF excluded autoimmune causes [2]. In literature reports of CNS involvement of chronic graft versus host disease exist, however, the patient did not meet the required criteria [3]. Patient got fully unconscious with preserved pain response, presented progressive tetraplegia, vanishing of deep reflexes, weakening of muscle tension with flaccid paralysis and continuous myoclonic seizures. The EEG showed slow basal activity of both cerebral hemispheres with generalized synchronic periodic sharp wave complexes and spikes within theta waves and suspicion of Creutzfeldt-Jackob Disease (CJD) was suggested. Finally, presence of 14-3-3 protein in CSF confirmed the diagnosis of CJD [4]. Since symptom onset the patient's neurological state deteriorated quickly within 6 weeks, death occurred within 4 months (Table 1).

The etiology of neurological alterations in patients after allo HSCT is very complex and differential diagnosis is difficult [3]. Creutzfeldt-Jackob disease is rare with morbidity approximately one per million per year [5]. While most probable, prion diseases make definitive diagnosis very difficult as they can occur spontaneously, be genetically linked or caused by inflammatory or contaminated transplant material [6]. As diagnosis of CJD is based mostly on exclusion it should always be considered as potential causes of rapidly progressing neurological disorders during careful survey of laboratory tests and picture examinations.

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