Simultaneous human herpesvirus 6-associated encephalitis and Guillain-Barré syndrome in a patient after matched unrelated donor haematopoietic stem cell transplantation

Agnieszka Tomaszewska1, Barbara Nasilowska-Adamska1, Tomasz Dzieciatkowski2, Bożena Marianska1

Abstract

Viral infections are still a serious diagnostic and therapeutic problem in patients undergoing alternative donor transplants. β-Herpesviruses (especially human herpesvirus type 5, 6 and 7) are recognized pathogens in this group of patients and may cause central nervous system disease. Guillain-Barré syndrome (GBS) is a very rare complication among stem cell transplant recipients and usually has been attributed to infection. We report a case of resolving simultaneous GBS and HHV-6-associated encephalitis in a haematopoietic stem cell transplant recipient with preceding reactivation of cytomegalovirus (CMV) infection. According to our knowledge this well-documented case is probably the first report from Poland.

Key words: human herpesvirus-6, encephalitis, Guillain-Barré syndrome, haematopoietic stem cell transplant recipients.

Introduction

Human herpesvirus type 6 (HHV-6) belongs to the subfamily β-herpesviruses and is closely related to human herpesvirus type 7 (HHV-7) and type 5 (HHV-5, formerly known as cytomegalovirus – CMV) [1]. All β-herpesviruses are emerging pathogens in haematopoietic stem cell transplant recipients (HSCT) and may cause central nervous system (CNS) disease [1, 2]. Diagnosis and treatment of CMV infection is currently more advanced than for HHV-6 and HHV-7 [1, 3]. Guillain-Barré syndrome (GBS), an autoimmune acute peripheral neuropathy, is a very rare complication among stem cell transplant recipients and usually has been attributed to infection [4, 5]. In this case report we present a patient with HHV-6 encephalitis complicated by GBS after matched unrelated donor stem cell transplantation with preceding reactivation of HHV-5 (CMV) infection. We also overview the treatment outcome in this patient. We received written informed consent from the patient for every invasive diagnostic procedure and for proposed therapy.

Case report

A 43-year-old man with a history of chronic myeloid leukaemia underwent HSCT from a matched unrelated female donor in October 2006...
after treosulfan-fludarabine-ATG conditioning. Sero-
status for CMV was IgG positive in the recipient and
IgG negative in his donor. On the 70th post-
transplantation day (PTD) the patient developed
aGvHD (acute graft versus host disease) I° with
skin involvement (generalised erythroderma) and
was successfully treated with intravenous (IV)
methylprednisolone [6]. On 8 March 2007 (the 149th
PTD) he was admitted to our unit due to CMV
infection reactivation (CMV DNA was 5523 geq/ml
and 8041 geq/ml in 2 consecutive examinations).
He started pre-emptive therapy with IV ganciclovir
according to the EBMT (the European Group for
Blood and Marrow Transplantation) standards [6, 7].

After 2 weeks of treatment he revealed high
fever (39.5°C), uroschesis (retention of urine),
paraparesis, impaired consciousness and
generalized epileptic seizure. Computed tomography
(CT) of his brain was normal. A lumbar puncture
revealed pleocytosis (24/μl) and elevated level of
protein (213.2 mg/dl). Investigation of cerebrospinal
fluid (CSF) by PCR (polymerase chain reaction)
methods for infective causes of the patient’s
neurological decline including HSV t.1/2 (herpes
simplex virus type 1/2), VZV (varicella-zoster virus),
adenoivirus, CMV and DNA Candida and Aspergillus
and Mycobacterium tuberculosis were negative as
well as CSF culture. Borreliosis and cryptococcosis
were excluded too. But real-time PCR (quantitative
commercial ALPCO MutaREAL HHV6 test) revealed
in his CSF presence of HHV6 DNA (215 geq/ml).
CMV DNA in blood samples was undetectable at
this time. Detection of anti-HHV-6 specific antibodies in IgM and IgG classes was performed,
using the commercial qualitative enzyme immunoassay (EIA) PanBio test. Our patient’s HHV-6
serology was IgG positive in the blood and negative
in the CSF (at the moment of diagnosis and after treatment) and IgM negative in every specimen.
According to these findings and the neurological
status of our patients we made a diagnosis of HHV-
6 encephalitis complicated by GBS. Therapy with
foscarnet (all symptoms revealed during pre-
emptive therapy with ganciclovir) and IVIG
(intravenous immunoglobulins) was started. Due
to GBS diagnosis we performed 5 procedures of
plasmapheresis followed by physical rehabilitation.
We observed gradual improvement in the
neurological status of our patient, but on 18 April
HHV-6 DNA was still detectable in control CSF ex-
amination (over 50 geq/ml). Nuclear magnetic
resonance (NMR) of our patient’s brain was performed – without any abnormal findings.
Negativisation of HHV-6 DNA in CSF was reached
on 26 April – after 20 days of foscarnet therapy.
After discharge the therapy was continued in the
outpatient clinic with cidofovir given once a week
for 4 weeks.

At present, 2 years after this episode, the patient
remains in a good condition without CMV
and HHV-6 reactivation, with only very slight
neurological deficiency.

Discussion

Human herpesvirus type 6 is the aetiologial
agent of exanthema subitum, a febrile rash illness
that can occur during early childhood [7]. After
primary infection, HHV-6 remains latent except for
periods of immunosuppression [7, 8]. Human
herpesvirus type 6 reactsivates in 33-48% of patients
who undergo HSCT and has been associated with
CMV infection, pneumonitis, myelosupression,
encephalitis and hepatitis [5, 7, 8]. Human
herpesvirus type 6 DNA is frequently detected in
blood during the first months after transplantation
in asymptomatic patients but not in CSF [6, 7].
There are 2 variants of HHV-6 A and B (HHV-6 A/B),
which differ from other human herpesviruses
because of the unique ability of their genomes to
integrate in a persistent latent state into
chromosomes (it is HHV-6 chromosomal integration
– HHV-6 CI). Human herpesvirus type 6 CI does not
represent active HHV-6 infection and its prevalence
in the population is described as 1-2%. In our case
we could not distinguish the HHV-6 variant because
the test used by us detects HHV-6 DNA without
specification of type. Clinical course, negative
results of HHV-6 DNA in blood and negativisation
of HHV-6 DNA in CSF of our patient allows us to
exclude HHV-6 CI and indicates HHV-6 B type as
a cause of this case of encephalitis. It is known that
HHV-7 is closely related to HHV-6 infection but its
detection after HSCT is relatively infrequent [7].
In our case we performed the HHV-7 DNA detection
test (major capsid protein [MCP] test) in the blood
and CSF retrospectively (on frozen samples) –
results were negative at the time of diagnosis and
after treatment. The only detected virus in the CSF
of the presented patient was HHV-6.

Over the last 15 years several reports describing
HHV-6-associated encephalitis in at least 48 HSCT
recipients have been published [2, 7, 9]. But the
association of HHV-6 encephalitis and GBS in the
HSCT setting has very limited observations [10].
Post-transplant GBS has usually been attributed to
infection and very rarely to neurotoxicity of
conditioning regimens [4, 10]. Approximately 75%
of patients show signs of infection shortly preceding
diagnosis of GBS [4, 10]. The detection of HHV-6 DNA
in CSF is a strong indication that the virus is actively
replicating within the CNS. An active HHV-6 infection
in the CNS during the clinical course of GBS suggests
that not only preceding but also concurrent
infections might be associated with GBS [10].

According to our knowledge this well-
documented and successfully diagnosed and
treated case of simultaneous GBS and HHV-6 encephalitis in a patient after HSCT is probably the first report from Poland. It is worth remembering that serology has no role in the diagnosis of HHV-6 infection in allo-SCT recipients; quantitative PCR for HHV-6 DNA is recommended for diagnosis of HHV-6 infection in peripheral blood or CSF [7, 11]. Due to its extraordinary sensitivity and rapid performance, real-time PCR guarantees detection of virus reactivation even if there is a low number of virus copies present in the sample. Early detection of HHV-6 infection with molecular biology methods is favourable for the efficacy of antiviral chemotherapy [11]. Foscarnet or ganciclovir are recommended as first-line therapies for HHV-6 encephalitis after HSCT and cidofovir as a second-line treatment [7, 11]. In our case HHV-6 encephalitis occurred during pre-emptive therapy with ganciclovir due to CMV reactivation, which was a diagnostic challenge.

In conclusion, simultaneous HHV-6 encephalitis and GBS is a very uncommon complication after HSCT. Our well-documented and successfully treated case indicates that HSCT recipients with CNS signs and symptoms should have their CSF investigated for HHV-6; and other infectious agents should be excluded by applying prompt and appropriate diagnostic tools such as culture, microscopy and PCR, especially real-time PCR. Also, exclusion of the phenomenon of HHV6 CI is required.

References