The Classic Form of Progressive Multifocal Leukoencephalopathy in Advanced Prostate Cancer: a Case Report

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Abstract
Progressive multifocal leukoencephalopathy (PML) is a serious and often lethal demyelinating disease of the brain that develops almost exclusively in patients with severe immunosuppression. The disease is caused by the reactivation of latent polyoma JC virus (JCV). PML occurs rarely in non-hematologic malignancies, and in this report, the authors present an uncommon case of rapidly progressing, fatal PML in a patient with advanced prostate cancer. Although uncommon, PML should be included in the differential diagnosis of white matter lesions in the oncologic population.

Keywords    Case report · MRI · PML · Prostate cancer

Introduction
Progressive multifocal leukoencephalopathy (PML) is a rare, devastating demyelinating disease of the central nervous system caused by the John Cunningham virus (JCV) in patients with compromised immune system [1]. JCV is a common polyomavirus named from the initials of the first patient from whom the virus was isolated in 1970 [1, 2]. Before the era of human immunodeficiency virus (HIV), PML remained a relatively rare condition occurring in few immunosuppressed patients, mostly with hematologic malignancies, organ transplant recipients, and patients with chronic inflammatory diseases [3]. In the recent years, HIV infection has become the most frequent immunodeficiency setting for PML, followed by hematologic malignancies, organ transplants, and patients with autoimmune diseases treated with immunomodulators [4, 5]. However, PML may occasionally develop in patients with minimal or occult immunosuppression, making the diagnosis particularly challenging [6]. In this report, we describe a rapidly progressive, fatal case of PML in a patient with prostate cancer, receiving several lines of standard therapy.

Case Presentation

The patient is an otherwise healthy 80-year-old Caucasian male with a history of advanced, castration-resistant prostate cancer. He underwent radical radiotherapy for his prostate tumor in 2010 followed by salvage prostatectomy 6 years later. Afterward, the patient developed multiple bone marrow metastases and received several lines of therapy including initial chemotherapy with docetaxel, subsequently shifted to enzalutamide and abiraterone due to progress of his cancer disease. Due to the known risks of hypokalemia and cardiac insufficiency induced by abiraterone, he received standard glucocorticoid replacement therapy with low-dose prednisolone and dexamethasone over the last 6 months. Prednisolone 10 mg once daily was given for the first 3 months and then switched to dexamethasone 0.5 mg twice daily.

Currently, the patient presented to the genitourinary cancer clinic with progressive mental deterioration including decreasing cognitive function, decline in memory, and episodes of acute confusion during the last few weeks. The neurological examination was otherwise non-contributory. Laboratory tests showed elevated C-reactive protein (CRP) level to 87 mg/l (normal range < 4 mg/l); however, white blood cells (WBC) count and differential were unremarkable.

Multiparametric 3-Tesla (3 T) magnetic resonance imaging (MRI) of the brain was performed and revealed large lesion within the left frontal lobe extending to corpus callosum and parasagittal part of right frontal lobe.
The lesion demonstrated predominantly high signal on fluid-attenuated inversion recovery (FLAIR) and T2-weighted sequences (Fig. 1a, b) and involves the subcortical white matter. There is restricted diffusion on the edge of the lesion (white arrows, c), while the central part predominantly shows an increased diffusion (c, d). Susceptibility weighted imaging (SWI) reveals no hemorrhage (e). Dynamic contrast enhanced (DCE) perfusion (f–h), time-dependent leakage \( K^\text{trans} \) perfusion map (i), and postgadolinium T1-weighted sequence (j) shows no enhancement. The lesion’s permeability curve is unspecific (k). A temporal resolution of 7.3 s was used when performing DCE enhancement (Fig. 1e–k). After the overall evaluation of morphological and functional sequences, PML was considered as the most likely diagnosis.

The cerebrospinal fluid (CSF) examination was performed and showed the prevalence of JCV with a viral load of 44,376 copies/ml CSF, confirming the PML suspicion. The disease had a rapidly progressive, fatal course,
and the patient died on June 4, 2020, a few months after the onset of symptoms.

Discussion

PML results in lytic infection of glial cells in the brain and is often fatal [3]. The disease is caused by the reactivation of JCV — a small, ubiquitous DNA polyomavirus that infects only humans [3]. After asymptomatic primary infection, which can occur in childhood, the virus remains silent in the kidneys, bone marrow, and lymphoid tissue [3]. The initial route of JCV infection is not well known, but is thought to be ingestion or respiratory inhalation [1]. More than 50% of the adult population is estimated to have been exposed [1]. A severe suppression in cellular immunity has classically been recognized as the absolute requirement for the reactivation of JCV; however, the disease has also been reported in patients with minimal or no initial clinically apparent immunosuppression [6]. The clinical symptoms can vary and are dependent on the location of demyelination areas in the brain.

Definitive (causative) diagnosis can only be made when PML is confirmed by histopathology (autopsy or biopsy of brain tissue) [4]. However, while histopathology is still the gold standard diagnostic criterion, imaging and laboratory tools are non-invasive, reliable, and suitable in daily clinical practice [4]. Diagnosis of PML is thus firmly established by the detection of viral deoxyribonucleic acid (DNA) or proteins in a brain biopsy or by the detection of JCV DNA in the CSF by polymerase chain reaction (PCR), together with typical imaging findings [3].

MR is the gold standard for the imaging of PML. Classic PML appears hyperintense on FLAIR and T2-weighted sequences and hypointense on T1-weighted sequences [3]. The lesions typically involve subcortical white matter and spare the cerebral cortex [3]. Occasional cortical and deep grey matter involvement can occur, but it is uncommon [1]. Multiple lesions are commonly present, and the distribution can be bilateral and asymmetric. Classic PML is devoid of edema, mass effect, or contrast enhancement on imaging [3]. DWI reveals an increase in diffusion in the center of lesions due to tissue injury and loss [4]. Instead, the periphery of expanding lesions shows a restrictive diffusion due to the presence of local inflammation and cellular infiltrates [4]. PML-immune reconstitution inflammatory syndrome (PML-IRIS) is another form of PML, which can develop during the recovery of the immune system. Unlike the classic PML, PML-IRIS can show the contrast enhancement on MRI due to the inflammation and breakdown of the blood–brain barrier [3]. The inflammation is usually associated with edema and mass effect [3].

As PML is associated with immunosuppression, the therapeutic aim is to restore the immune function of the host [4]. There is no specific antiviral drug against JCV, and PML still remains a fatal disease with no specific treatment [3]. Cancer is the predisposing factor for PML; however, this complication occurs rarely in oncological patients, being mostly reported in hematologic malignancies. To our knowledge, this is the first report describing development of PML in a patient with prostate cancer, receiving standard treatment. In our patient, the combination of several factors presumably contributed to reactivation of JCV and subsequent brain infection, such as advanced cancer disease, long-lasting castration, steroid replacement, and chemotherapy.

Conclusions

Although uncommon, PML should be kept in mind when assessing white matter lesions in the oncologic population. PML typically occurs in patients with severe immunosuppression; however, one should be aware that this disease can infrequently develop in those with minimal or clinically occult immune compromise [6].

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Declarations

Ethics Approval and Consent for Publication Informed consent was obtained from the patient’s family member prior to the submission of this report.

Consent to Participate Not applicable.

Conflict of Interest The authors declare no competing interests.

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