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Progressive multifocal leukoencephalopathy: an unexpected complication of modern therapeutic monoclonal antibody therapies

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disorder of the central nervous system, caused by the reactivation of the ubiquitous JC virus. PML usually occurs during severe immunosuppression, and the most common causes are represented by human immunodeficiency virus infection, lymphoproliferative disorders and other forms of cancer. Recently, the introduction of monoclonal antibodies (e.g. natalizumab, rituximab, efalizumab) in the treatment of several dysimmune diseases such as multiple sclerosis, rheumatoid arthritis, psoriasis and systemic lupus erythematosus, has led to an increased incidence of PML. This phenomenon has had severe consequences, leading, for example, to the withdrawal from the market of Efalizumab, and important restrictions in the use of the other compounds, all of which are characterized by high efficacy in improving prognosis and quality of life. In this review we will discuss clinical, laboratory and imaging findings of PML. In addition, proposed pathogenetic mechanisms promoting the reactivation of JC virus in the context of treatment with monoclonal antibodies will be described.

Keywords: Efalizumab, monoclonal antibodies, natalizumab, progressive multifocal leukoencephalopathy, rituximab
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Introduction

The definition 'Progressive Multifocal Leukoencephalopathy' (PML) was first used in 1958 to describe a fatal demyelinating central nervous system (CNS) disease in patients with lymphoproliferative disorders [1]. In 1971, the virus responsible for the disease was isolated and named JC virus (JCV) after the initials of the patient from whom the virus was first isolated [2]. After 40 years, several aspects of the disease are well known but many questions regarding the pathogenesis remain unanswered and no effective treatment is available. In the pre-human immunodeficiency virus era PML was anecdotally reported in some patients with myelolymphoproliferative disorders or other forms of cancer, but its incidence significantly increased with the advent of acquired immunodeficiency syndrome, affecting 0.7/1000 persons/year [3]. After the introduction of antiretroviral treatment the incidence (0.07/1000 persons/year) [3] and the mortality of the disease reduced significantly [4,5]. Recently, several cases of PML related to the use of new immunomodulatory compounds for the treatment of several dysimmune diseases were reported, leading to an urgent need for the identification of risk factors and disease biomarkers.

Pathogenesis

JC virus is a double-stranded, circular DNA virus and a member of the Polyomaviridae family. The viral genome encodes six viral proteins, including two early regulatory regions (small and large T antigens), another regulatory protein acting as a viroporin (agnoprotein) and the capsid pro-

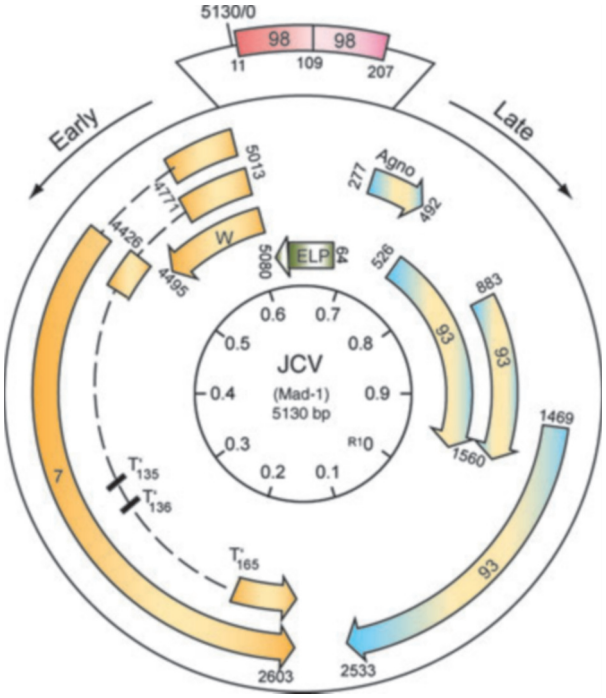

FIG. 1. JC virus circular DNA encodes for early transcripts, including small and large T antigen and for late proteins (capsid proteins VP1, VP2, VP3 and agnoprotein).

teins (VP1, VP2 and VP3) (Fig. 1). The presence of rearrangements in the highly variable non-coding control region characterizes the so-called Mad-1 type strain, neurotropic and pathogenic, which probably derives from the non-pathogenic archetype, detected in kidneys and tonsils.

There are two main hypotheses regarding the route of primary infection, involving either upper respiratory tract through inhalation or the gastrointestinal tract through ingestion of contaminated food and water. The finding of JCV in tonsils seems to support the former hypothesis [6], but the virus has also been detected in epithelial cells from the gastrointestinal tract [7,8] and in the oesophagus [9]. However, as JCV can infect circulating B lymphocytes, both tonsils and gastrointestinal tract may represent a site of latency rather than the entry route of the virus. After the primary asymptomatic infection, which is thought to occur in childhood, the virus remains latent in different sites, including kidney—as demonstrated by the shedding of virus in the urine of 30% of immunocompetent subjects [10]—bone marrow [11], B lymphocytes [12] and tonsils [6]. There is recent evidence that the virus enters the brain from the early phases of infection and establishes a non-productive or low-chronic infection of glial cells [13,14]. Under particular conditions, usually associated with severe immunosuppression, JCV can actively replicate into the brain, leading to PML. The site and modality of JCV reactivation are still poorly understood but the most likely hypothesis is that the virus reactivates somewhere in the periphery and crosses the blood–brain barrier through circulating infected cells, such as B lymphocytes, entering the CNS where it infects astrocytes and promotes lysis of oligodendrocytes with a consequent massive demyelination, predominantly involving white matter.

Clinical Findings

The classic form of PML has a fulminating evolution usually leading to death within a few months. The onset is usually multisymptomatic and the most common clinical presentation includes motor deficits, altered consciousness, gait ataxia and visual symptoms. Atypical presentations, usually reported in human immunodeficiency virus-infected patients after the introduction of combination antiretroviral therapy, include pure cerebellar syndrome, reflecting a productive infection of granule cell neurons [15], meningitis [16], meningoencephalitis [17,18], progressive myoclonic ataxia [19] and muscle wasting associated with extrapyramidal signs [20].

Histopathological and Imaging Findings

Histopathology findings are typically represented by demyelination, enlarged oligodendrocytes productively infected by the virus as demonstrated by appropriate staining, and bizarre astrocytes [21]. Foamy macrophages may be found at the advancing edge of the lesions, actively involved in the removal of myelin breakdown products [22]. Inflammation is usually little or absent. Conventional magnetic resonance imaging shows an extensive involvement of white matter, with multifocal, bilateral, asymmetrical lesions that appear hyperintense in T2-weighted sequences and hypointense in T1-weighted sequences (Fig. 2). The pathogenetic process starts from the subcortical white matter and evolves towards the deep periventricular regions, involving also thalamus and basal ganglia, with coalescence of lesions in the mid-to-late stage [23]. Parieto-occipital lobes are preferentially involved [24]. Infratentorial white matter is frequently affected, with lesions located in the middle cerebellar peduncles and adjacent regions, e.g. pons and mid-cerebellum [25]. As inflammation is uncommon, oedema and contrast enhancement are atypical findings.

Laboratory Findings

The diagnostic criteria recently proposed require the detection of the virus in cerebrospinal fluid by PCR [22]. The sensitivity of this laboratory technique was 72–92% in the