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RESEARCH ARTICLE

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Pomalidomide-Associated Progressive Multifocal Leukoencephalopathy (PML) in a Patient with IgG-κ Multiple Myeloma (MM)

Cassataro G[1]*, Smorlesi G[2], Miceli G[1,4], Ruscica F[2], Alaimo V[3], Volpe V[1], Burlon R[1], Fertitta E[1], Canale C[1], Tomaiuolo L[1], Stella M[1], Grimaldi LM[2] and Renda M[1]

[1]Department of Internal Medicine, Fondazione Istituto "G. Giglio", Cefalù.
[2]Department of Neurology, Fondazione Istituto "G. Giglio", Cefalù.
[3]Department of Radiology, Fondazione Istituto "G. Giglio", Cefalù.
[4]Department of Health promotion, Mother and Child Care, Internal Medicine and Medical specialties (ProMISE), Università degli Studi di Palermo, Palermo.

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Introduction

Progressive multifocal encephalopathy (PML) is a rare demyelinating disease of the central nervous system (CNS), caused by reactivation of the John Cunningham virus (JCV), which affects mainly immunocompromised individuals [1]. The JCV is common in the general population, up to 50-60% in some studies [2]. It remains quiescent in the kidneys, bone marrow and lymphoid tissue after asymptomatic infection in childhood [1]. Whenever the physiological immune surveillance becomes deficient (eg. treatment with monoclonal antibodies in chronic inflammatory diseases, HIV infection, hematological malignancies) [3], the virus escapes the immune control and undergoes some mutations in its genome [2], transforming itself into a neurotropic form potentially leading to a lytic infection of glial cells [1,4]. If not early detected, the disease is almost invariably fatal, as the only effective treatment so far is the restoration of the immune system, where possible [5]. We describe a case of PML in a Pomalidomide-treated patient for multiple myeloma. So far, 16 cases of PML have been reported in patients with multiple myeloma, only 2 of which were associated with Pomalidomide therapy [6].

Case Description

A 76-year-old woman, with a past medical history of hypertension and postoperative hypothyroidism, had been suffering from multiple myeloma IgG-κ (stage ISS II) since 2005. She came to our attention due to a left sensorimotor hemisyndrome, which had arisen about three months earlier. The symptoms had started subtly, with a slowly progressive course, and became so serious as to impair gait. At the time of admission, the patient had recently stopped chemotherapy due to severe leukopenia (PMN < 500/uL). Until that moment she had been on the third-line therapy with a pomalidomide-dexamethasone-cyclophosphamide regimen for eighteen monthly cycles. The brain CT performed in the Emergency Room showed a hypodense lesion in the subcortical white matter of the right frontal and parietal lobes, of unclear significance. On neurological examination she was alert and aware, oriented in space and partially disoriented in time. Her language was fluent and the cranial nerves unaffected. Moderate to severe brachio-crural hemiparesis with slight spastic hypertone was present, and mild global homolateral hypoestesia. She could not stand up on her own. The patient was then admitted to the Internal Medicine Unit for further investigations. The initial course was complicated by pneumonia requiring non-invasive ventilation, and by a catheter-associated bloodstream infection. She was seronegative for human immunodeficiency virus. Despite recovery from such illnesses, her neurological conditions worsened, with complete left hemiplegia and hemineglect, progressive dysarthria evolving to mutism, dysphagia, and impaired degree of consciousness. Magnetic resonance of the brain (MRI) showed a bulky and uneven hyperintense lesion in the T2/FLAIR sequences, extending to the subcortical white matter of the right hemisphere, with well-defined border towards the cortex and involvement of the U-fibers. An initial spread to left hemisphere was already present at that time. The lesion was hypointense in the T1 sequence, and showed no gadolinium contrast enhancement (figure 1). A suspicion of possible PML was made, considering the very typical MRI alterations [7] and the congruent clinical presentation. The lumbar puncture showed a clear cerebrospinal fluid (CSF) with normal amount of glucose and protein, and absence of malignant cells. The real-time polymerase chain reaction (PCR) for the presence of JCV DNA in the CSF provided positive result (609.234 copies/mL). Definite PML associated with pomalidomide was diagnosed. As chemotherapy had already been suspended about two months earlier, no trial with plasmapheresis was considered indicated. Actually, the degree of progression of the disease was already advanced enough to make any therapeutic attempt useless. For this reason, only supportive therapy was administered. The

Contact: Giuliano Cassataro, Department of Internal Medicine, Fondazione Istituto "G. Giglio", Cefalù.

patient eventually died about two months after the diagnosis had been made. For this article we obtained the informed consent of the patient's daughter, who in the meantime had been appointed as her legal representative.

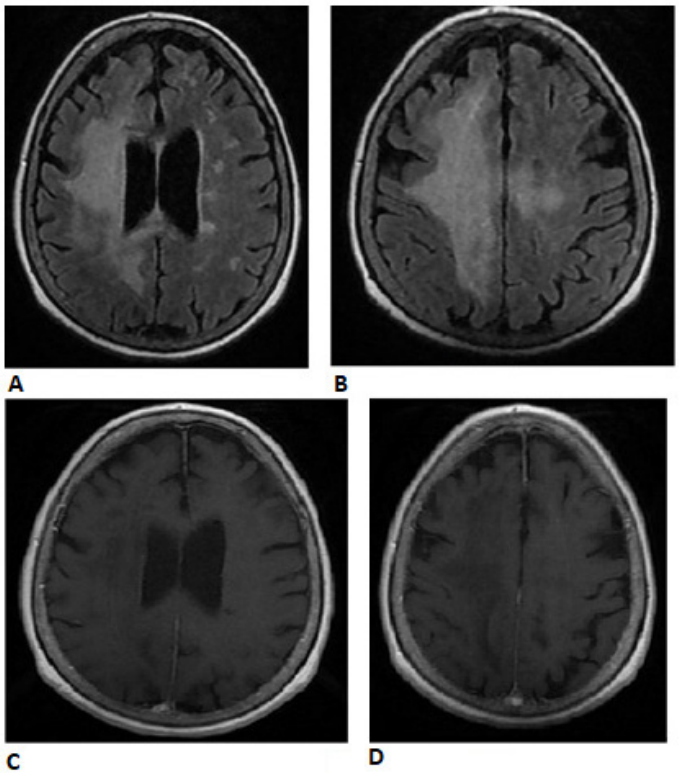

Figure 1 : (**a-b**) Magnetic resonance imaging T2 fluid-attenuated inversion recovery (FLAIR) showing bilateral asymmetric hyperintense lesions with typical subcortical and periventricular distribution and involvement of the U-fibers; (**c-d**) The lesions are hypointense and non-enhancing on post-contrast T1 images.

Discussion and Conclusions

Multiple myeloma is a haematological neoplasm whose impact has greatly increased in the last few decades [8]. Worldwide incidence has increased by 126% since 1990, while mortality has increased by 94%, with the largest rise in the low-middle income countries where the access to effective care is very limited [9]. It is a complex condition in which both natural history and available therapies lead to immunosuppression with an augmented risk of developing opportunistic infections such as PML [10]. Immunomodulatory drugs (IMiDs) possess numerous anti-myeloma properties [11], but they are also burdened with the risk of developing PML [12]. To date, pomalidomide-associated PML is exceptionally rare, probably because it is a more recent drug [6]. Actually, the therapeutic regimen of our patient also included cyclophosphamide, whose association with PML is also known [13]. Multiple sclerosis patients treated with Natalizumab (NTZ) undergo routine screening for JCV VP1 antigen-directed antibodies. Thus, those who are at greater risk of developing PML are followed up more closely, with repeated brain MRI examination every three months. Thanks to this protocol, the risk of NTZ-associated PML has been much better controlled in recent years [14]. On the other hand, in multiple myeloma, as well as other risk conditions for PML, there are no adequate screening programs [3]. In these populations the incidence of PML is greatly underdiagnosed and patients are often older than those with multiple sclerosis, a condition which may lead to a poorer prognosis [15]. In conclusion we encourage the implementation of screening programs in all patients at risk for PML, trying to prevent this potentially devastating disease. Although further clinical studies are needed, the stratification of asymptomatic JC virus carriers with serological tests could be a valid initial strategy, also considering its good cost-benefit ratio. In those patients at greater risk, routine use of neuroimaging and neurological advice could increase the chances of an early diagnosis.

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