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CASE REPORT

HPV-associated Anal and Genital Intraepithelial Neoplasia After Using Fingolimod in the Treatment of Relapsing-remitting Multiple Sclerosis: A Case Report

Melis Doganay Ocalan[1], Gulin Morkavuk[1], Asli Yarci Gursoy[2], Suleyman Ozdemir[3], Alev Leventoglu[1]

[1]Ufuk University Faculty of Medicine, Department of Neurology, Ankara, Turkey
[2]Ufuk University Faculty of Medicine, Department of Gynecology and Obstetrics, Ankara, Turkey
[3]Ufuk University, Faculty of Medicine, Department of General Surgery, Ankara, Turkey

Abstract

Multiple sclerosis (MS) is a chronic, autoimmune, neurodegenerative disease of the central nervous system, with inflammation and loss of myelin in axons. Fingolimod is the first oral disease-modifying agent approved for the treatment of relapsing-remitting MS. Here we aimed to present a patient with MS who developed human papillomavirus (HPV)-associated anal and genital intraepithelial neoplasia while on fingolimod treatment. A 19-year-old female patient presented with the complaint of diplopia. The diagnosis of MS was made based on imaging and cerebrospinal fluid results. She was treated first with beta-interferon 1a, then methotrexate, and finally fingolimod. While the patient was being followed without attack under fingolimod treatment, HPV-associated genital, and further, anal warts developed. This is a rare case that developed both cervical dysplasia and anal Condyloma acuminatum due to the HPV that developed after fingolimod treatment in a patient with MS. In conclusion, fingolimod treatment increases the risk of cervical HPV infection and related cancer in patients with MS.

Keywords: Multiple sclerosis, relapsing-remitting, fingolimod, HPV, cervical dysplasia

Introduction

Multiple sclerosis (MS) is a chronic, autoimmune, neurodegenerative disease of the central nervous system. Various immunomodulatory treatment strategies are available, which differently affect the immunological settings in MS pathology. Today, early initiation of disease-modifying therapies (DMT) is beneficial over the long term, resulting in a significant disability reduction. Fingolimod is the first oral immunomodulatory agent that has recently been used for the treatment of relapsing-remitting MS (RRMS) and is a functional S1P analog that acts as an antagonist to S1P receptors (1). After oral administration, the molecule undergoes phosphorylation and binds to the S1P receptor, thereby internalizing and degrading the receptor. Lymphocytes are separated from the lymphoid tissue due to S1P activation, and fingolimod secondary decreases the circulating lymphocyte levels in the absence of this activation (1). Reported side effects include symptomatic bradycardia, macular edema, and liver dysfunction. Rare neoplasms while on fingolimod treatment, such as melanoma, uterine leiomyoma, Bowen's disease, breast cancer, Kaposi's sarcoma, and thyroid cancer, have been reported in case reports (2). Human papillomavirus (HPV) infection can be cleared from the body through the immune system. However, it can cause permanent infections in people whose immune response is insufficient. Additionally, persistent infections are also associated with high-risk oncogenic HPV-related cervical, anal, vulvar, vaginal, penile, and oropharyngeal cancers (3). Herein, we will discuss the young female patient with MS treated with fingolimod and known HPV with varying degrees of cervical, vulvar, and anal dysplasia.

Case Report

Our female patient was diagnosed with RRMS aged 19-years-old, after presenting with a diplopia complaint. Her neurological

Address for Correspondence: Gulin Morkavuk, Ufuk University Faculty of Medicine, Department of Neurology, Ankara, Turkey
Phone: +90 505 508 82 56 **E-mail:** drgcmor@yahoo.com **ORCID-ID:** orcid.org/0000-0001-7522-8585
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examination revealed a 4/5 muscle strength in the right lower extremity, normal sensory examination, hyperactive deep tendon reflexes, and bilateral extensor plantar response. Cranial and cervical spine magnetic resonance imaging showed lesions typical of inflammatory demyelination. The cerebrospinal fluid analysis showed Type-2 oligoclonal bands. She was commenced on a first-line DMT in the form of subcutaneous beta-interferon 1a that lasted for 2 years. Further, she was treated with methotrexate and pulse methylprednisolone IV every month (both together) between 2012 and 2014. Unfortunately, she continued to have relapses; thus, escalation to fingolimod was initiated in 2014. Her lymphocyte count before starting treatment was 1.8×10^9/L and her varicella-zoster virus immunoglobulin G was positive. At the 3-month followup, she had become lymphopenic, as expected, with a lymphocyte count of 0.5×10^9/L. During the 6 years following the fingolimod administration, she was relapse-free and without significant disability (EDSS=1.5). Additionally, lymphocyte values ranged between 0.3×10^9/L and 0.6×10^9/L. However, when she reached 30 years, she developed genital warts that responded to cryotherapy treatment and were periodically assessed by a dermatologist and gynecologist. Additionally, a few months later, she developed anal warts. Her general surgeon resected the lesions twice but she stayed on fingolimod. The gynecological examination detected multiple millimetric condylomas in the vulvar region. A cervical smear was taken for the first time and an HPV vaccine was recommended. The cytological examination was reported as "low-grade squamous intraepithelial lesion" and HPV screening was positive for high-risk HPV types other than 16 and 18. Colposcopic examination revealed multiple suspicious lesions, and cervical biopsies, including endocervical curettage were held. Histopathological examination was reported as "high-grade squamous intraepithelial lesion" at 3 locations without endocervical involvement. The patient was treated with a loop electrosurgical excision procedure, and the histopathological examination of the conization specimen was reported as cervical intraepithelial neoplasia (grade 2) at multiple locations with disease-free surgical margins. Anal inspection at the same session revealed perianal condilomatous lesions, which all were excised and histopathologically reported as anal intraepithelial neoplasia I.

Fingolimod was discontinued and all lesions resolved within a month. One month after drug discontinuation, a new attack developed with sudden vision loss and right hemiparesis. She was treated with intravenous methylprednisolone for 10 days. Approximately 2 months after the fingolimod cessation, the patient started natalizumab therapy while maintaining a stable neurological condition and had no further wart recurrence since natalizumab is a humanized monoclonal antibody that inhibits the passage of activated T-cells, B-cells, and monocytes across the blood-brain barrier and has no effect on peripheral lymphocyte count.

Written and informed consent was obtained from the patient for publication of this case report.

Discussion

HPV is the most common sexually transmitted disease worldwide. The broad majority of sexually active males and females are affected at some point in their lives (4). The immune system has a fundamental role in the spontaneous recovery phase, and immunosuppressive drugs may be the major risk factors for persistent HPV infection. Generally, HPV infections are cleared by the host immune system within 1-2 years in the majority of cases. Only 10-15% of cases develop persistent infection leading to cancer, if not managed and treated appropriately and promptly (5). Scientific data about the effect of fingolimod treatment on HPV infection is unavailable; however, a few cases were reported in the literature regarding the possible promoting effects of fingolimod on HPV reactivation and genital dysplasia (3). However, a case series of 16 patients with no previous HPV infection who developed HPV lesions after starting fingolimod was published in 2021. Of these patients, 6 discontinued fingolimod, and the HPV vaccine was administered (6). The other mentioned cases were on fingolimod treatment for ~17-58 months and did not respond to conventional treatments for benign/malign warts until the drug dose was modulated or discontinued (3). Our case had been receiving fingolimod treatment for 72 months at the time of diagnosis and the dose was not modulated due to its high effectiveness on MS.

Despite the strong immunomodulatory effects of fingolimod, it was not associated with significantly increased other infections in phase III clinical studies, except for varicella-zoster and herpes simplex virus (1,7). Additionally, the increased cutaneous malignancy rates are thought to be associated with fingolimod, and dermatological examination is recommended before treatment initiation (8).

The exact mechanism of action of fingolimod in patients with MS is unknown, by interacting with S1P receptors, it prevents the release of lymphocytes from lymphocyte tissue (8). S1P inhibition leads to cancer cell growth, nutrients and oxygen supplication for tumor formation, and process regulation, such as inflammation that triggers neovascularization (7). Concerns regarding the use of fingolimod increased due to the risk of prolonged lymphopenia and associated infections (1). The proper functioning of the immune system prevents HPV infection from becoming permanent. Herein, the role of T and B lymphocytes is great. The decreased lymphocyte count during fingolimod treatment may not provide the necessary immune response during HPV infection. Therefore, we think that the infection may become permanent and turn into neoplasia in this case (5).

The effect of fingolimod on cellular immunity, which is favorable for MS treatment might be an emerging risk factor for high-risk females with positive HP that deserves further attention. HPV infection, previous gynecological history, and screening test evaluation might have value before starting up fingolimod treatment (3). Primary prevention through HPV vaccination reduces the frequency of HPV-related neoplasms (9).

Conclusion

Therefore, studies have shown that immunosuppressant drugs can increase the risk of cancer in patients with MS. We wanted to contribute to the literature with this case of cancer, which we think is caused by the effect of fingolimod. We think that cervical screening, pap smear, gynecological examination, and HPV vaccination programs before fingolimod treatment in patients with MS are important. However, more research is needed to better understand the risks and other known risk factors regarding the duration and type of immune therapy in females with autoimmune disease.

Ethics

Informed Consent: Written and informed consent was obtained from the patient for publication of this case report.

Authorship Contributions

Surgical and Medical Practices: A.Y.G., S.O., A.L., Concept: G.M., A.L., Design: A.Y.G., S.O., A.L., Data Collection or Processing: G.M., A.Y.G., S.O., A.L., Analysis or Interpretation: G.M., A.L., Literature Search: M.D.O., G.M., Writing: M.D.O., G.M., A.L.

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