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LETTER TO THE EDITOR

How to detect cervical dysplasia due to fingolimod use?

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Fingolimod is a nonselective sphingosine-1-phosphate (S1P) receptor modulator[1] used in the treatment of relapsing-remitting multiple sclerosis. Sphingosine-1-phosphate inhibition may alter the regulation of inflammation and neovascularization, which may predispose to malignancy. Sphingosine-1-phosphate receptor modulators also reduce the capacity of lymphocytes to egress from lymph nodes, leading to reduced lymphocytes in peripheral blood.[1] Hence, the intrinsic cancer surveillance may be impaired, and the immune defense against viral oncogenesis can be reduced. Regrettably, lymphopenia, severe infections, and malignancy are among the significant adverse events of S1P receptor modulators.[1]

Human papillomaviruses (HPVs) are responsible for 96.6% of cervical cancers.[2] Although the underlying mechanism has not been fully explained, the possible causal link between HPV-associated neoplasm and fingolimod was reported.[1,3,4] Herein, we presented a case highlighting the importance of periodic gynecological follow-ups during fingolimod treatment in the context of possible HPV-associated malignancy.

A 28-year-old female patient with relapsing-remitting multiple sclerosis received interferon beta-1a treatment for eight months. Since three attacks occurred in one year under treatment with interferon beta-1a, she was switched to fingolimod 0.5 mg once a day. Before fingolimod treatment, routine blood tests and cardiac, ocular, dermatological, and gynecological examinations, including a Papanicolaou (Pap) smear, were performed. Neither visible genital warts nor documented pathological findings were evident. Additionally, the patient had no prior vaccination history for HPV infection. The lowest lymphocyte count was 300/µL (normal range, 1000-4000/µL) during the first six months of treatment, and it remained within the normal range thereafter. A written informed consent was obtained from the patient.

While on fingolimod, the patient was attack-free and continued to have annual gynecological examinations without any gynecological complaints or remarkable Pap smear screen results. At the six-year gynecological follow-up, the routine Pap smear revealed a high-grade squamous intraepithelial lesion (H-SIL), and an excisional procedure was scheduled. The final pathological report revealed Grade 3 cervical intraepithelial neoplasia (CIN 3), with negative surgical margins in the excisional material, requiring close annual surveillance. Fingolimod, as a suspected factor of cervical dysplasia, was discontinued, and the patient was switched to teriflunomide. Written informed consent was obtained from the patient.

Cervical cancer ranks among the leading malignancies in the female genital tract. The major pathogenic factor responsible for this cancer is high-risk types of HPV. These viruses activate oncogenic genes, leading to excessive cellular proliferation and, over time, dysplastic changes. In healthy women, the immune system typically eliminates these high-risk strains within one to three years.[2] However, certain conditions

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that impairs the immune system may cause the persistence of high-risk HPV types in cervical tissue. If this persistence continues, it increases the risk of dysplastic changes, as approximately 10% of cervical infections turn into chronic diseases and may lead to low- or high-grade squamous intraepithelial lesions[2] and, finally, to malignant transformation.

Impaired immune response to viruses associated with fingolimod may cause the increased rates of chronic HPV infection. While a causal link has not yet been proven, previous case reports and series suggested an increased susceptibility to the HPV-associated genital wart, condyloma, and cervical and anogenital cancer during fingolimod treatment.[3,4]

Considering the reduced immune defense against viral infections and the decreased cancer surveillance in fingolimod-treated patients, vaccination against HPV and regular Pap smear testing are recommended.[5] This applies only to fingolimod among the S1P modulators.[1] On the other hand, since the vaccines do not cover all HPV subtypes, and given the older fingolimod-treated patients with MS, screening for HPV-associated diseases remains essential.

Herein, we reported that a patient under fingolimod had no gynecological complaints or symptoms but was diagnosed with H-SIL during a periodic gynecological examination. This lesion was surgically removed, and fingolimod treatment was discontinued as a precaution. Our patient was in the sixth year of fingolimod treatment, which was in keeping with the report of Mhanna et al.[3] In the study of Mhanna et al.,[3] including 16 patients with MS with HPV lesions, HPV lesions were noted to appear four years (range, 0.2 to 12 years) after the onset of fingolimod. Nine of these patients had cervical dysplasia, five had low-grade squamous intraepithelial lesions, and four had H-SIL. As in our case, fingolimod was discontinued due to severe HPV disease in six of 16 patients.[3]

Clinicians should be vigilant for HPV-associated lesions in fingolimod-treated patients with MS. Early recognition of HPV-associated lesions could help lessen the risk of progression to cancer. Ultimately, in light of the literature and in the context of this case, we advocate for routine gynecological screening in patients receiving fingolimod.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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