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Case report

# Cutaneous anaplastic large cell lymphoma in a multiple sclerosis patient receiving Fingolimod

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ABSTRACT

*Background:* Previous reports of cutaneous neoplastic lesions secondary to Fingolimod treatment among multiple sclerosis patients.
*Objective:* Reporting a case of cutaneous large cell lymphoma in a multiple sclerosis patient during Fingolimod treatment.
*Method:* Case study.
*Result:* Our patient developed CD30+ cutaneous large cell lymphoma two years after initiation of Fingolimod treatment and her symptoms regressed following the cessation of treatment.
*Conclusion:* This report indicates that cutaneous lymphoid neoplasms should be considered a possible side effect among patients receiving Fingolimod.

## 1. Introduction

Fingolimod is an oral immunomodulatory drug that is used for the treatment of multiple sclerosis (MS). It prevents disease relapse and progression through inhibition of B and T lymphocytic release from the peripheral lymph nodes into the circulation and subsequently the central nervous system (Kappos et al., 2015). The most important side effects of Fingolimod are liver enzyme elevation and macular edema. Other commonly reported side effects include nasopharyngitis, headache, and fatigue followed by cardiac arrhythmia and reactivation of neurotropic viruses (Kappos et al., 2015; Minagar, 2013).

There have been a few mentions of cutaneous side effects due to Fingolimod treatment such as opportunistic skin infections and cutaneous malignancies (Behle et al., 2016; Carpenter et al., 2017; Conzett et al., 2011; Walker and Brew, 2016). Here we present a rarely reported side effect of MS treatment with Fingolimod leading to cutaneous anaplastic large cell lymphoma.

## 2. Case report

A 42-year-old female multiple sclerosis patient referred to our neurology clinic (Kashani hospital, Isfahan, Iran) for routine follow up examinations. She was diagnosed with relapsing-remitting MS since 2009 after an episode of left-sided hemiparesis and optic neuritis and was treated primarily with Beta interferon 1b (Betaferone, BAYER pharma). Other important medical history included an episode of severe cutaneous reaction (Stevens-Johnson syndrome) to Carbamazepine and subsequent hospitalization, 10 years ago.

Currently, she was not receiving any other medications other than MS treatments. Due to repeated MS relapses, patient's treatment was changed to Fingolimod (Fingolide, OSVAH pharmaceutical) since two years ago; the treatment was tolerated well and relapse rates had decreased; no liver insufficiency or visual side effects was reported during this time. The patient did not have any complaints regarding the disease symptoms throughout this time. During the examination interview, she only complained of having a painful itchy spot on the right shoulder. Neurologic examinations of the patient revealed no new findings; subtle paresthesia of the left hand and arm was present. Systemic examinations were also normal; however, upon examination of her back, the patient had a 1 cm by 1 cm mass on her right shoulder blade near the tip of the scapula (Fig. 1a). The mass was firm and without fluctuation, it was clearly circumscribed, had no attachment to the underlying tissue and was elevated 5 mm above the surrounding skin. No ulceration, scaling, discharge or pigmentation was seen regarding the mass or the surrounding skin.

The patient was referred for a dermatology consultation and was scheduled for more detailed tests and a skin biopsy. Skin pathology reported a diffuse infiltration of lymphoid cells in dermis and subcutis

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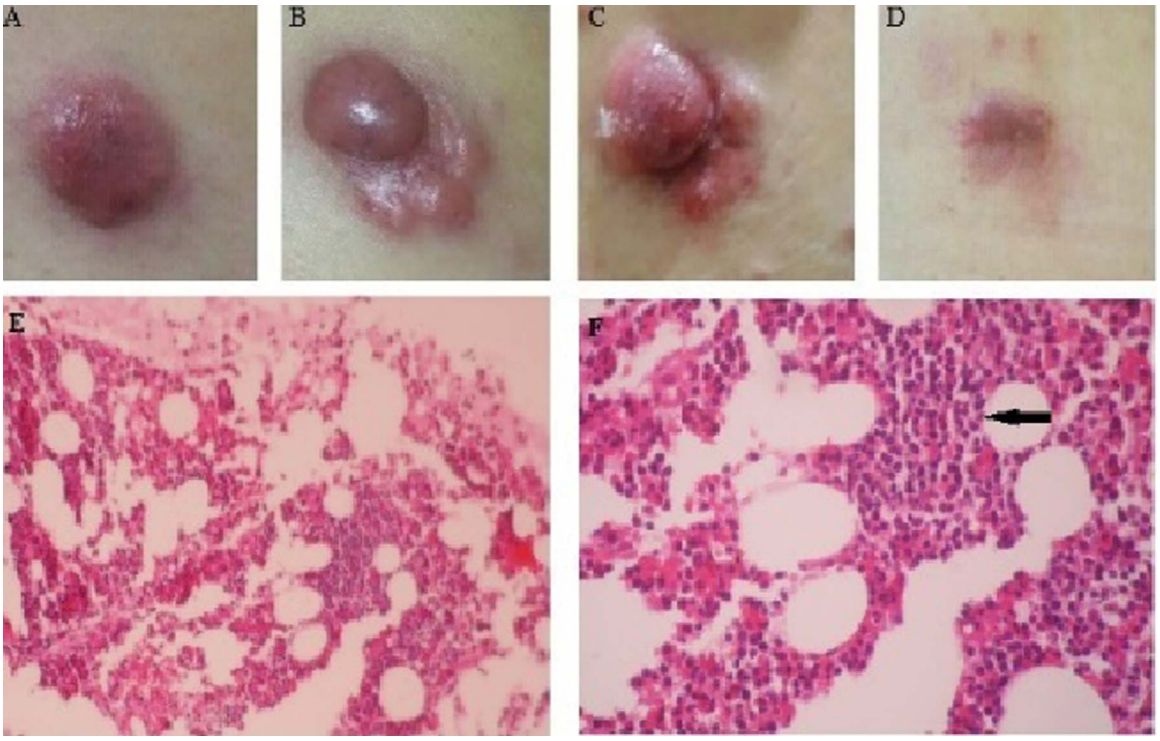


**Fig. 1.** The progressive states of the cutaneous lesion; A: primary presentation, B and C: gradual progression of the lesion during assessment time and development of secondary lesions, and D: Post biopsy/after the cessation of Fingolimod treatment. Histology of the lesion (× 10-E) and (× 40-F). Black arrow: Small non paratrabecular lymphocytic nodule.

composed of cells with enlarged and prominent oval nuclei and 1–2 mitotic figures per each HPF (Fig. 1e and f). Based on the report cutaneous anaplastic large cell lymphoma was suggested for the patient. Immunohistochemistry tests revealed CD30 positive cells; these cells were also positive for CD3 and CD4 and they were negative for CD20, CD10, CD8, and CD7; the Ki-67 index was 80%. Blood cell count values were normal (WBC: 5.08 × $10^3/\mu m^3$, RBC: 4.05 Mil/$\mu m^3$, Platelet: 170 × $10^3/\mu m^3$). In order to rule out bone marrow involvement, bone marrow aspiration/biopsy was performed; normal cellularity with trilineage hematopoiesis was reported; mild increase in lymphoplasma cells in smears was seen (12–14%) and multiple small non para-trabecular lymphocytic nodules were observed. Biochemical values were within normal range and chest, abdomen and pelvis imaging was negative for space-occupying masses in bones and soft tissue organs, infiltrations, effusions and lymph node involvement.

Based on the findings, cutaneous anaplastic large cell lymphoma was confirmed for the patient. The cutaneous mass was growing during the assessment period and developed secondary smaller lesions on its borders (Fig. 1). With the cessation of Fingolimod as the suspected triggering agent, the growth of the tumor was stopped. Upon visit after a 2-month follow-up, all the lesion had regressed and no new lesions were formed.

## 3. Discussion

Fingolimod is second line oral immunomodulatory drug for relapsing MS; considering that it has recently been approved and administered relative to other MS treatments, possible previously unknown side effects are vital to be recognized.

To the best of our knowledge cutaneous anaplastic large lymphoma is rarely mentioned as a side effect of Fingolimod treatment and we found only one account of a similar report (Papathemeli et al., 2016). Skin-related side effects of Fingolimod treatment varies in type including opportunistic infections such as Molluscum contagiosum and cryptococcosis (Behle et al., 2016; Carpenter et al., 2017), endothelial function disruption causing ecchymosis and neoplastic lesions (Masera et al., 2014). These side effects were more frequently seen with higher doses of treatment during primary trials and high dose regimens are not encouraged in clinical practice (Doggrell, 2010). Fingolimod induced skin lesions are reported in other previous studies as melanoma (Conzett et al., 2011; Robinson and Guo, 2016), Kaposi sarcoma (Walker and Brew, 2016) and cutaneous anaplastic large cell lymphomas (Papathemeli et al., 2016) as well as lymphomatoid papulosis (Samaraweera et al., 2016). Regarding the mechanism through which Fingolimod could have contributed to the incidence of such tumors, Papathemeli et al. have reported a similar case, claiming that Fingolimod treatment may cause unchecked malignancies such as melanoma and lymphoma due to its effects on CD4 positive T cells (Papathemeli et al., 2016). Considering the similarity of cell surface markers in our case to the Papathemeli report, the time before symptoms had started after treatment with Fingolimod in both cases and positive response to discontinuation of the drug, it could be suggested that both cases are examples of a similar phenomenon and that such an event could be expected to occur in other instances as well. The pattern of disease emergence and resolution in correlation to Fingolimod administration supports the connection between Fingolimod and the cutaneous anaplastic large cell lymphoma as its side effect.

Since the cutaneous form of anaplastic large cell lymphoma is able to further develop into more aggressive systemic diseases with more severe clinical outcomes it is advisable that physicians consider this disease during the follow up of patients receiving Fingolimod.

## Declaration of conflict of interest

The authors declare that there is no conflict of interest.

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