Lymphomatoid papulosis in a patient treated with glatiramer acetate and the glatiramoid Glatopa for multiple sclerosis: A case report

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ABSTRACT

A 48-year-old Caucasian woman with history of multiple sclerosis (MS) presented with erythematous papulonodular lesions in her extremities and trunk. She was being treated with glatiramer acetate (GA) for the past 10 years and the glatiramoid, Glatopa, for 2 years prior to this presentation. A skin biopsy showed CD30+ lymphoproliferative disorder consistent with lymphomatoid papulosis (LyP). Three weeks after stopping Glatopa, her skin lesions were improved. It remains unclear whether GA’s or Glatopa’s capability to alter T-cell differentiation, may have a link with LyP. This case report is a reminder to be vigilant for skin lesions in patients with MS.

KEYWORDS: Lymphomatoid papulosis, multiple sclerosis, glatiramer acetate, glatiramoids, giotapo, skin

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Case report

A 48-year-old Caucasian woman with history of relapsing-remitting multiple sclerosis (MS) – diagnosed at age 26 – presented with multiple non-itchy non-tender erythematous papulonodular lesions over her extremities, and trunk (Figure 1, panels A-C). She denied any preceding fever, infections, insect bites, or medication changes. She was being treated with glatiramer acetate (GA) and a glatiramoid for the past 12 years. She was initially on branded GA (Copaxone®) for 10 years, and later was switched to the glatiramoid, Glatopa®, 2 years ago. Prior to GA, she was not exposed to any other MS disease modifying therapies (DMTs). A skin biopsy, 6 weeks after the eruption onset, showed CD30+ lymphoproliferative disorder suggestive of lymphomatoid papulosis (LyP) (Figure 1, panels D-F). On physical examination, there was no palpable organomegaly or lymphadenopathy. She was further evaluated for any evidence of systemic malignancy. Flow cytometry analyses of peripheral blood identified no neoplastic cells. CT scan of chest, abdomen, and pelvis revealed no occult malignancy. In the absence of any evidence to suggest systemic lymphoma, a bone marrow biopsy was not pursued, and the diagnosis of LyP was confirmed. Glatopa was discontinued. A brain and cervical cord MRI at the time of Glatopa discontinuation showed interval radiological progression compared to a prior MRI.

About 3 weeks after stopping Glatopa, an improvement in her skin lesions became noticeable. Subsequently, natalizumab therapy was initiated.

Written informed consent was acquired from the patient for clinical information and medical images to be published.

Discussion

CD30+ lymphoproliferative disorders are the second most common form of cutaneous T-cell lymphomas behind mycosis fungoides.1 These disorders comprise a spectrum including LyP, primary cutaneous anaplastic large-cell lymphoma (pcALCL), and borderline or indeterminate cases.1 LyP is a rare disease with an estimated prevalence of 1.2-1.9 cases per million. It presents as chronic, recurrent, self-healing papulonodular skin eruptions.2 Patients with LyP overall have a very good prognosis; however, 15-20% of them may develop a second malignancy in long-term such as mycosis fungoides, pcALCL, or Hodgkin lymphoma.1 The etiopathogenesis of LyP remains to be elucidated. Triggering factors may include radiation therapy or certain immunotherapies. CD30+ lymphocytes can be seen in a wide range of inflammatory and reactive disorders and other lymphoid neoplasms that may mimic LyP clinically and histologically. Therefore, appropriate
Clinicopathologic correlation is essential for an accurate diagnosis of LyP. Glatiramer acetate, formerly known as co-polymer-1, is a mixture of synthetic polypeptides composed of 4 amino acids resembling the myelin basic protein. The immunomodulatory effects of GA and glatiramoids in MS are primarily attributed to their capability to alter T-cell differentiation, and induce a shift from a pro-inflammatory Th1 pattern to an anti-inflammatory Th2 pattern. Glatiramer acetate and glatiramoids have mitogenic effects on T cell subsets, which theoretically may predispose susceptible recipients to lymphoproliferative disorders. Of note, CD30 is a T-cell-costimulatory molecule involved in the regulation of the balance between Th1 and Th2. Both GA and glatiramoids, known for inducing a shift towards Th2, may disturb this balance. Potential adverse effects of GA and glatiramoids are mostly tissue-specific and include injection site erythema and lipoatrophy. There have been very rare reports of cutaneous malignancies with GA. Our literature review showed no published report of LyP associated with GA or glatiramoids; however, 1 case report of CD30+ pcALCL was described in a 33-year-old woman 4 months after initiating GA. It remains unclear whether GA's capability to alter T-cell differentiation may have a link with cutaneous T-cell lymphomas. Two cases of LyP in association with fingolimod use in MS were reported. In 1 case, LyP developed 2 months after initiating fingolimod, and resolution began only 2 days after stopping fingolimod. In another case, the eruption began within 2 years after starting fingolimod. There has been 1 case report of LyP 6 months after initiating dimethyl fumarate (DMF). This is perhaps unusual in that DMF has been shown to inhibit tumor growth and is being investigated as a treatment for cutaneous T-cell lymphoma. Our literature review failed to show any reports of LyP in MS patients exposed to anti-CD20+ therapies. However, LyP exacerbation was reported during rituximab treatment in 2 patients with lymphoma suggesting that altered B-cell cytokine milieu by anti-CD20+ therapy may exacerbate concomitant T-cell disorders such as LyP.

In our patient, it remains uncertain whether GA or Glatopa triggered LyP, or whether it was the cumulative use of both agents, or a mere coincidence. A recurrence of LyP following a re-challenge with the potential causative agent may confirm this relationship, however in view of the potential risks, and non-optimal control of her MS disease activity, we avoided a re-challenge with Glatopa. Therefore, no causality can be inferred from the association between GA or Glatopa and LyP in this case report.

**Conclusion**

This case reminds us to maintain vigilant for skin lesions in patients with MS treated with DMTs. Occurrence of LyP is also important to recognize in order to better understand the T-cell modulator effects of DMTs in other organ systems such as the skin.
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