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Peer Review Report for "Relapse in Alopecia Totalis after Successful Treatment with Intralesional Corticosteroid and Oral Immunomodulator"

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Review Timeline:

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Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0)

12 May 2020

Dear AE,
This is an interesting case presentation, and still important for daily medical practice. Since alopecia areata is quite common worldwide, pieces of information about the aetiopathogenesis, devolution and treatments of the hair disease are of avail. However, values and the real relevance of treatments should be more explained and censorious discussed - taken into consideration the potential of spontaneous recovery of alopecia areata.
Thanks.

REFEREE: Reviewer | **Revision** (0)

14 May 2020

Dear AE,
It is an interesting case report but the authors had multiple treatment modalities, so the role of oral Inosine pranobex is suspicious, thus report of another case with inosine therapy alone is more acceptable.
Thanks.

REFEREE: Reviewer | **Revision** (0) 15 May 2020

Dear AE,
The manuscript contains 2 abstracts. the authors should specify only one.
Thanks.

REFEREE: Associate Editor | **Revision** (0) 18 May 2020

Dear EIC,
The manuscript needs minor revision.
Thanks.

REFEREE: EIC | **Revision** (0) 18 May 2020

Dear Author,
Your article is reviewed by the reviewers carefully. According to their comments, this document needs minor revision. Please follow their comments as requested.
Thanks.

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Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Relapsing in Alopecia Totalis after Successful Treatment with Intralesional Corticosteroid and Oral Immunomodulator

Abstract:

Introduction: Alopecia areata (AA) is a chronic, recurrent, and non-scarring hair loss which may affect all hair-bearing area. There are three clinical patterns: patch AA, alopecia totalis and alopecia universalis. Patients may show spontaneous recovery or good response to the treatment, but the disease may follow a course of relapse.

Case presentation: We report a case of recurrent alopecia totalis following a successful treatment six years prior visit. A 19-year-old Asian female was admitted to our clinic due to recurrent hair loss in the last three months. Six years prior visit, she was diagnosed with alopecia totalis. After four years of remission, she started to have patchy hair loss. Dermatological examination revealed six nummular well-defined alopecia patches all over her parietal, temporal and occipital scalp. She was treated with triamcinolone injection and light-emitting diode (LED). Moreover, topical minoxidil and hydrocortisone butyrate scalp solution were applied daily. Oral Inosine pranobex was administered twice a week. One year after the first re-administration of the therapy, complete remission was achieved.

Conclusion: Relapse in AA is common. It should be informed during education and counseling. Long term follow-up is essential in managing patient with AA.

Keywords: alopecia areata, immunomodulatory, intralesional corticosteroid, trichoscopy

Introduction

Alopecia areata (AA) is a common type of alopecia in human and the second most frequent non-scarring alopecia after male and female pattern alopecia ([1]). Alopecia areata is chronic, recurrent and non-scarring hair loss which may affect all hair-bearing area ([2],[3]). There are three clinical patterns of AA, which is a clinical spectrum: a small patchy bald lesion (patchy AA) that can progress to a total loss of scalp hair (alopecia totalis) and total loss of body hair (alopecia universalis) (1,3).

Formerly, numerous hypotheses on the etiology of alopecia areata have been proposed, such as infection, trophoneurotic hypothesis (emotional/physical stress and/or trauma), intoxication, thyroid disease and hormonal change (1). In 2001, Madani et al. emphasized genetic and immunological factors as the main factors since the peribulbar lymphocytic infiltration was proven although emotional/physical stress and infection might precipitate AA (2). Less or more, AA is an autoimmune disease which onset and progression are unpredictable. Spontaneous hair re-growth is estimated to occur in 80% of patients within a year after the incidence of alopecia but relapse can occur at any stage ([4]).

Alopecia areata is not easily managed medically ([5]). To date, there is no FDA-approved treatment for AA. There are range of topical, intralesional and oral therapeutic options but neither are curative nor preventive. Patient may show spontaneous recovery or good response to the treatment, but the disease may follow a course of relapse ([6]). We reported a case of recurrent alopecia totalis following a successful treatment six years prior visit.

Case Presentation

A healthy 19-year-old Indonesian female visited our dermatology clinic with chief complaint of patchy hair loss in the last three months. Six years prior visit, she was diagnosed with alopecia totalis in our clinic (**Figure 1a-b**). Laboratory findings revealed high titer of anti-cytomegalovirus and anti-rubella IgG. A 4-mm punch skin biopsy was performed six years ago on the scalp and showed notable perifollicular and perivascular lymphohistiocytic infiltrate.

Before first meeting with us, the patient had visited several doctors. We treated the patient with topical minoxidil, and adding triamcinolone acetonide injection once in two weeks, oral valacyclovir, oral inosine pranobex and light-emitting diode (LED) therapy which previously were not given to the patient. Starting four months, patient had already showed satisfying regrowth response. Patient In two-year-period of follow up, the response was satisfying with complete hair re-growth (**Fig 1 c-d**). After four years of remission, she started to have patchy hair loss. The hair loss was getting worse for the last three months.

Dermatological examination revealed six nummular-sized well-defined alopecia patches all over her parietal, temporal and occipital scalp (**Figure 2a**). Trichoscopic findings showed black dots, exclamation mark hair, short vellus hair and upright re-growing hair (**Figure 2b**). Laboratory findings show

increased anti-cytomegalovirus IgG titer (128.4 AU/mL) and anti-rubella IgG titer (34.3 IU/mL).

Patient was re-treated with triamcinolone injection, oral inosine pranobex, topical minoxidil, hydrocortisone butyrate scalp solution and LED. Triamcinolone injection and LED were administered once in a two-week period. Topical minoxidil and hydrocortisone butyrate scalp solution were applied daily. Oral Inosine pranobex was administered twice a week. After one month of treatment, patient showed marked improvement in the number of daily hair shedding and the alopecia patches' size. The bald lesions were completely regressed after seven months of therapy although the hair density in the previously bald area was still less than in the normal area (**Figure 3 a-c**). One year after the first re-administration of the therapy, complete remission was achieved.

Discussion

Diagnosis of AA was established through the nature of the disease, clinical and trichoscopic findings. Trichoscopy is a useful diagnostic tool for the diagnosis and monitoring hair and scalp diseases. The trichoscopic features in alopecia areata are yellow dots, black dots, exclamation mark hairs, tapered hairs, broken hairs, short vellus hair, upright re-growing hair, and etc (2). In this patient, we found black dots, exclamation mark hairs, and upright re-growing hairs, which have a mean prevalence of 53%, 39% and 23%, respectively. In our case, the patient experienced recurrent patchy hair loss after four-year period of remission. Intralesional triamcinolone and topical minoxidil were chosen as the first line therapies (1). Light emitting diode therapy was also administered every two weeks since this therapy had been proven to be effective. Two studies from Lanzafame et al. had found that LED significantly improved hair regrowth in both men and women alopecia ([7],[8]). The usage of LED therapy is safe and also already approved by FDA. ([9])

Patient presented 6 years prior with alopecia totalis. The patient had several attributes for poor prognosis including extensive hair loss (alopecia totalis), early age onset, duration of onset more than 1 years, and resistant to standard therapy of alopecia ([10]). We added inosine pranobex in this cases since the etiopathogenesis of AA is immune-related (3,[11]). Inosine pranobex, or commonly known as isoprinosine or methisoprinol, is an immunomodulatory agent which have been studied as potentiator of T- cell lymphocytes and phagocytic cell function. Since defective in cell mediated immunity is suggested

possessing critical role in alopecia areata ([12]), several studies found beneficial in alopecia areata treatment. In a double-blind randomized controlled trial of single treatment of inosine pranobex in recalcitrant alopecia androgenetic conducted by Georgala et al. (2006) showed in treatment group there were 5 (33.3%) had full remission, 8 (53.3%) responded partially and 2 (13.3%) did not respond meanwhile in control group 4 (28.5%) responded partially and 10 (71.4%) did not respond. The therapeutic effect was statistically significant ($\chi 2=7.82$, $p<0.01$) (10). Another study by Galbraith et al. followed patients with AA for 1 year where 8 patients responsive to inosine pranobex therapy from 17 treated patients. The patient who responded to the treatment also had corelated skin biopsy results with significant T cell enhancement ([13]). Lowy et al studied 20 patients with AA including alopecia totalis whom 14 of them treated with inosine pranobex. Nine patients responded to the treatment. Nonetheless, seven patient which responded previously had autoantibodies which diminished after treatment ([14]). Although the second course of AA also responded well to therapy, relapse is unpredictable (2,3,6). The rapid onset of hair loss and disfigurement of AA may cause anxiety and psychological stress. Therefore, education and counseling play an important role in managing AA (4). Since the course of relapse is unpredictable, it is essential to do long-term follow-up to manage and evaluate the progression of AA.

Since patient was treated with multiple treatment in this study, it is impossible to singled out performance of treatment modalities. However, addition of inosine pranobex, intralesional steroid injection, and valacyclovir were leading to patient clinical improvement despite the poor prognostic factors.

Spontaneous remission could not be ignored as AA is remain unpredictable with several cases could be normalized spontaneously ([15]). In this patient's case when patient first visited with alopecia totalis 6 years prior, the possibility of spontaneous remission is as low as 8% considering involvement of >50% of the scalp. Nonetheless, bad prognostic factors including early age onset, duration of onset more than 1 years, and resistant to standard therapy of alopecia might decreased the probability of spontaneous remission in this patient (9). When patient visited with patchy alopecia areata however, the involvement of scalp with less than 25% area had higher 68% chance of spontaneous remission ([16]).

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Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) 27 May 2020

Dear AE,
The manuscript has been now added and completed concerning all comments and proposals of the reviewers.
Thanks.

REFEREE: Associate Editor | **Revision** (1) 2 Jun 2020

Dear EIC
Based on the authors' answers to the reviewers' comments, the reviewer(s) have recommended publication.
Kind regards.

REFEREE: EIC | **Revision** (1) 2 Jun 2020

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.