

SHORT PAPER



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Is rituximab therapy a risk factor for development of melanoma?

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Abstract

In the literature, there are reports about dermoscopic and size changes of nevi in patients undergoing biologic therapy and chemotherapeutics. There has not been any established data for melanoma and Rituximab therapy. Sixteen patients, with 94 nevi were included in this study. Dermoscopic images of follow-up visits, which were performed at baseline, 3, 6, and 12 months after treatment, were evaluated. Suspicious lesions were excised. There was no increase in total nevus count. Although 61.7% of the 94 nevi have shown a stable duration without size changes, 26.5% had enlarged, and 11.7% had become smaller during our 1-year experience of dermoscopic monitoring. There was not any pattern transformation. Atypical dots and clods appeared in 17% of nevi. All of the excised nevi were comparable with Clark nevi, there was no clue for melanoma development. According to our results, we found that Rituximab therapy influences nevus morphology, but there is no evidence that this was linked to melanoma development.

KEYWORDS

dermoscopy, nevus, rituximab

1 | INTRODUCTION

Traditional immunosuppressive drugs, such as glucocorticoids, cyclosporine, methotrexate, and azathioprine cause the global immunosuppression. Biologic therapies selectively target cells and pathways of the immune system to achieve specific therapeutic effects and are used primarily in the treatment of rheumatic, inflammatory, and malignant diseases.

Rituximab is a chimeric immunoglobulin (Ig) G1 CD20-specific monoclonal antibody. The primary use of rituximab is in the treatment of B-cell malignancies and in selected autoimmune disorders, including rheumatoid arthritis, autoimmune cytopenias, autoimmune skin disease (pemphigus, pemphigoid), Sjögren syndrome, and some forms of vasculitis. Rituximab depletes peripheral blood B cells, and subsequent normalization of B cell numbers typically requires 6 to 9 months or longer.

Dermoscopic changes with TNF- α inhibitors have been investigated.¹ The effects of rituximab on the nevi and development of melanoma have not been elucidated up to now. The aims of our study

include changes in nevus count, nevus size, and dermoscopic changes in patients taking rituximab therapy.

2 | MATERIALS AND METHODS

The dermoscopic images evaluated in this study were collected in the database of the Department of Dermatology of the Bezmialem Vakif University. Ethical approval was obtained from the local ethics committee. In total, images of melanocytic nevi were obtained from 16 patients (females and males). One of the 16 patients had pemphigus vulgaris and the other patients had Hodgkin lymphoma. One patient was pemphigus vulgaris, received two intravenous (IV) infusions of rituximab 1 g on days 0 and 14, the other patients received four doses of 375 mg/m² weekly.

Dermoscopic evaluations at each visit were performed using a computerized polarized-light video dermoscopy system (FotoFinderdermoscope, Teachscreen Software, Bad Birnbach, Germany) with an alcohol interface solution. Dermoscopic images of

follow-up visits, which were performed at baseline, 3, 6, and 12 months after treatment, were evaluated. Dermoscopic changes in lesions were evaluated by the observation of two groups of changes in subsequent visits, changes in size and changes in color, to determine their dermoscopy scores. Atypical dermoscopic features were the multicomponent pattern (more than one dermoscopic pattern), atypical pigment network, irregular dots and globules, irregular projections, white scarring, blue-white veil, reverse pigment network, milky red areas, atypical vascular structures (multiple vascular pattern).² The nevi which got had one of these atypical dermoscopic changes, or changes in color, and size during the study, were excised and histopathological examination was performed.

3 | RESULTS

There was no increase in total nevus count. Ninety-four nevi from 16 patients were enrolled in the study: 9 (56.2%) male and 7 (43.8%) female. The mean age of the patients was 56.4 ± 4.62 (min: 36, max: 76). Nine patients had Fitzpatrick skin type 3 and 7 had Fitzpatrick skin type 4. The most common dermoscopic patterns were reticular (48 nevi; 51%), homogeneous (28 nevi; 29.7%), and globular (12 nevi; 12.7%).

Although 58 (61.7%) of the 94 nevi have shown a stable duration without size changes, 25 (26.5%) of the 94 nevi had enlarged, and 11 (11.7%) of the 94 nevi had become smaller during our 1-year experience of dermoscopic monitoring. There was not any pattern transformation.

Color changes were observed in 5 of 16 patients. Four nevi were fading in color (4.2%). Nine of the nevi darkened in color (9.5%).

Atypical dots and clods appeared in 7 patients (43.7%), and 16 of 94 nevi (17%; Figures 1-4). Atypical pigment network was appeared in three patients (20.8%). These lesions were excised and the histopathological results were comparable with Clark nevus, there was not any clue for development of melanoma.



FIGURE 1 Nevus on the baseline

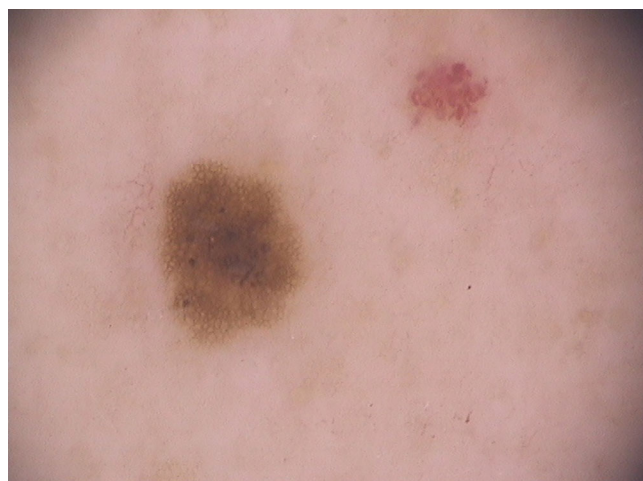


FIGURE 2 Nevus after 1 year treatment with rituximab, appearance of clods

4 | DISCUSSION

Rituximab, a chimeric immunoglobulin G1 (IgG1) monoclonal antibody (mAb), is used to treat lymphoproliferative disorders and several rheumatic diseases. It is usually administered as a short series of typically two or four intravenous infusions every 4 to 6 months or at longer intervals as needed.

Common acquired melanocytic nevi begin to appear after the first 6 months of life, increase in number during childhood and adolescence, reach a peak count in the third decade, and then slowly regress with age.^{3,4}

The "outbreak of pigmented moles" was first described by Hutchinson in 1868, and several reports have since been published.⁵ "Eruptive melanocytic nevi" (EMN) is commonly used to describe the phenomenon of a sudden occurrence of multiple new moles. EMN was suggested to be triggered by diseases in 50% of cases or



FIGURE 3 Nevus on the baseline



FIGURE 4 Nevus after 1 year treatment with rituximab, enlargement of nevus and appearance of clods

by drugs in 41% and were either idiopathic or miscellaneous in 9%. Most cases were associated with skin diseases, especially blistering diseases.⁶

According to Koseoglu et al, as well as there is a statistically significant increase in nevus numbers in the treatment group compared with the control group, that increase was specifically significant in the anti-TNF- α , methotrexate, and azathioprine groups compared with baseline. These results are comparable with reports indicating that immunosuppressive therapy increases the number of acquired melanocytic nevi.⁷ But, in our case group, we did not find any differences between the baseline nevus count and after the treatment with 1 year rituximab therapy.

BRAF (v-raf murine sarcoma viral oncogene homolog B1) is a serine/threonine-protein kinase that plays a critical role in the RAS-RAF-MEK-ERK mitogen-activated protein kinase (MAPK) cell signaling pathway. BRAF inhibitors and MEK inhibitors (BRAFi) (MEKi) affect this pathway.⁸

Perier-Muzet et al reported BRAFi therapy induces mainly hyperpigmentation, whereas combination treatment with BRAFi and MEKi causes global pigmentation. Two patients showed no dermoscopic changes, however, two patients with atypical nevus syndrome exhibited more than 70% of variations, and they suggested that some patients are more sensitive to the targeted therapies.⁹

Another report by Yamamura et al showed the effect of nivolumab on dermoscopy. The monoclonal antibody nivolumab blocks programmed death-1 (PD-1), an inhibitory immune checkpoint receptor expressed on activated T cells. They observed depigmentation on melanoma macule, after eight courses of nivolumab. Using dermoscopy, their observation revealed peppering inside the depigmentation area of a primary melanoma lesion after the successful treatment with nivolumab. They suggested that depigmentation may be due to a reduction in epidermal melanocytes, which can be accompanied by T-cell infiltration in the skin during immune responses induced by immune checkpoint blockade therapy.¹⁰

TNF- α inhibitors and immunosuppressive agents which are used for the treatment of inflammatory diseases, cause an increase in nevus size for all nevi,¹ but rituximab caused enlargement in 26% of nevi. This difference may be related to distinct mechanism pathways of TNF- α inhibitors and rituximab. TNF- α inhibitors, change the cytokine environment, by the way, rituximab is effective by B cells.

Depigmentation was observed in a melanoma patient undergone nivolumab therapy,⁹ but only 4% of nevi had faded in our study. Nivolumab binds PD-1 with high affinity, blocks its interactions with both PD-L1 and PD-L2, and stimulates memory response to tumor antigen-specific T-cell proliferation. Rituximab is a chimeric monoclonal antibody that targets the CD20 molecule on the surfaces of normal and malignant pre-B and mature B lymphocytes. Rituximab kills B cells by multiple mechanisms of action, including complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity, which are immune-mediated mechanisms, as well as by direct effects on cell signaling pathways and cell membranes following CD20 binding. As a result of B cell reduction, depigmentation, fading in color may not be significant in these patients.

In spite of known associations of immunosuppressive therapy and melanoma risk, development of eruptive nevi, and proposed mechanisms for such risks, this study did not demonstrate any increased risk of melanoma or eruptive nevi. All of the excised lesions were benign.

In conclusion, under Rituximab therapy, 26% of nevi had enlarged and atypical dots and clods appeared at 17% of nevi. With respect to the secondary outcome of histopathologic evaluation, 16 lesions were excised, because of dermoscopic change during the study. All were benign. Although this study showed that Rituximab therapy influences nevus morphology, there was no evidence that this was linked to melanoma development. Further studies are needed to confirm our results.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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