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Vitiligo following intravitreal ranibizumab: An association or an unrelated event?

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Abstract

Age-related macular degeneration (ARMD) is the most common cause for visual impairment in the elderly in western countries. Its incidence in India is expected to increase with the increase in the size of geriatric population. Recently several anti-vascular endothelial growth factor (VEGF) drugs like pegaptanib sodium (Macugen), ranibizumab (Lucentis) and bevacizumab (Avastin) are available for use in the management of wet ARMD. Besides being too expensive, long term results of these drugs are not available as of now. A 65 yrs old patient diagnosed with wet ARMD was given intra-vitreal Ranibizumab. He developed vitiligo involving both hands post injection. To the best of our knowledge this is the first reported case Ranibizumab- induced vitiligo. It not only draws attention to the fact that VEGF receptors have an important role in pathogenesis of vitiligo but also to the commonly ignored area of systemic side-effects of intra-vitreal anti-VEGF therapy.

Keywords: Anti-VEGF therapy, Vitiligo, Ranibizumab.
Key Message: This study highlights the fact that intra-vitreal anti-VEGF therapy has many yet unreported systemic side-effects which need to be explored. It also underlines the role of VEGF receptors in pathogenesis of vitiligo.

Introduction

Anti-VEGF agents have been shown to be safe and effective when given intravitreally to patients with neovascular wet age-related macular degeneration (ARMD). As of now long term results of these drugs are not available, and the only dermatological side effect reported so far, is one reported case of subcutaneous lupus erythematosus resulting from use of Ranibizumab.(3) A 65 yrs old patient diagnosed with wet ARMD was given intra-vitreal Ranibizumab, developed vitiligo involving both hands post injection. To the best of our knowledge this is the first reported case Ranibizumab- induced vitiligo. It not only draws attention to the fact that VEGF receptors have an important role in pathogenesis of vitiligo but also to commonly ignored area of systemic side-effects of intra-vitreal anti VEGF therapy.

Case History

65 years old patient of wet ARMD received two intra-vitreal ranibizumab (in a dose of 0.5 mg in 0.05 ml) as one month interval. Patient was asymptomatic in the follow-up period of 6 months. After six months patient received two doses of ranibizumab (one in each eye). All injections were performed under standard sterile conditions. Three days after injection the patient presented with hypo-pigmented lesion on the dorsal aspect of both the upper limbs as shown in Fig. 1. Lower extremities, trunk, head and neck and groin area was also examined but no similar lesions could be identified. Laboratory studies demonstrated normal hemoglobin, hematocrit, thyroid stimulating hormone, and thyroxine. Hence, vitiligo associated with either pernicious anemia or thyroid disease was excluded. In addition, there was no personal or family history of thyroid disease or pernicious anemia.

The patient was seen by a dermatologist who confirmed vitiligo lesions lesion on the dorsal aspect of both the upper limbs. Patient was observed for a month but did not show any change in size, shape or the numbers of the lesions. The patient did not complain of generalised lightening of his skin after starting of Ranibizumab treatment. The wet ARMD responded well to the intra-vitreal ranibizumab. Patients received two more intra-vitreal injections of the same drug and followed up for next three months. The patient had another dermatology evaluation after three months in which it showed persistence of his ranibizumab induced vitiligo that had originated after the initiation of his ranibizumab therapy.

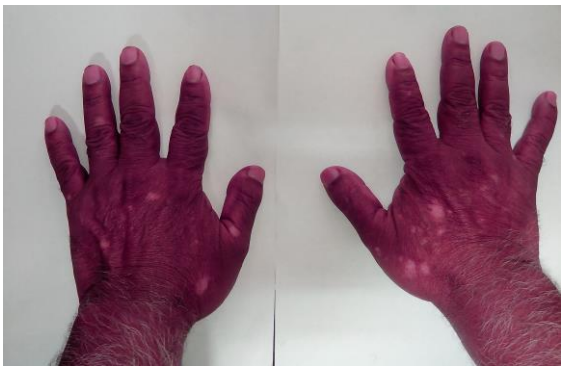

Fig. 1

Discussion

Vitiligo results from autoimmune-mediated destruction of melanocytes and it typically presents as amelanotic macules and patches that are symmetrically distributed. Affected areas often include distal digits and periorificial sites. Several hypotheses have been proposed to explain the pathogenesis of vitiligo; some

of them include genetic factors, neurologic factors, toxic metabolites, and lack of melanocyte growth factors.[4]

In vitiligo, vascular endothelial growth factor (VEGF) recptors and angiogenesis plays an important role in its pathogenesis. It is documented that the epidermis is thicker than in normally pigmented and that inflammatory changes are more frequent and intense in the epidermis and dermis of perilesional skin. Moreover angiogenesis, vascular endothelial growth factor(VEGF) positive cells and mast cells are increased in the center compared to the periphery. Angiogenesis accompanied by epidermal hyperplasia, is a histological finding observed also in psoriatic lesions. In psoriasis the morphological alterations of the blood vessels are prior to visible epidermal hyperplasia accompanied by lymphocytic infiltration. It is interesting to note that systemic anti-VEGF treatment strongly reduces skin inflammation in a mouse model of psoriasis.[5]

In vitiligo, temporal correlation between increased angiogenesis and epidermal hyperplasia in the center of the lesion is not noted, where there is almost no lymphocytic infiltration. The loss of melanin leads to the above histopathological changes in the end stage of vitiligo, whereas its presence is important to maintain the normal cutaneous histological picture.[6]

Patients with anti-neoplastic agent-induced vitiligo have been described. Neither a specific class of anti-neoplastic drugs nor a unique tumor origin or histology has been associated with the development of cutaneous hypopigmentation. Similarly, antitumor drug-associated vitiligo has not been linked to a specific route of administration; cancer therapy-related hypopigmentation has occurred following not only intravenous administration of the agent, but also oral, subcutaneous, and topical delivery of the drug. The onset of drug-induced vitiligo has been found to occur as early as a couple of days to as long as 6 months after the associated medication has been started. No associated side effects of intravitreal ranibizumab were encountered like vitreous haemorrhage, pain, floaters, inflammation. There was no change in vitiligo following the doses of the drug and the vitiligo was status qua. The patient was prescribed topical mometasone with multivitamin supplementation and was observed for the first three months. No change in the size or color of lesions seen. No biopsy or tyrosinase receptor analysis was done. Drug-induced vitiligo has also been associated with antineoplastic agents including doxorubicin, imatinib, imiquimod, interferonalpha, interferon beta, interleukin-2, interleukin-4, mitoxantrone, and surviving inhibitor. The development of chemotherapy associated vitiligo is not a drug-limiting side effect in patients whose cancer is responding to the agent. Additionally, vitiligo has persisted in many of these individuals even after discontinuation of the associated drug.[7] Similar observations are made in our patient.

It is interesting to note that the VEGF and EGFR pathways are found to be closely related, sharing common downstream signaling pathways in the growth and dissemination of tumors.[8] Furthermore, EGF, a key EGFR ligand, is one of the many growth factors that drive VEGF expression.[9] Biological agents targeting the VEGF and EGFR pathways have shown clinical benefit in several human cancers, either alone or in combination with standard cytotoxic therapies. Inhibition of VEGF-related pathways is thought to contribute to the mechanism of action of agents targeting the EGFR.[10]

There was no sign suggestive of malignancy. Blood investigations done to rule out excessive cellular turnover because of some occult malignancy included complete blood count, serum lactate dehydrogenase (LDH), serum uric acid, serum urea, serum creatinine. These were within normal limits. It was not a dose related side effect because it neither progressed nor regressed with subsequent doses of drug. It might be an idiopathic reaction or an unrelated coincidental finding with ranibizumab. The exact mechanism of genesis of vitiligo could not be established in this case. In the light of above mentioned facts these anti VEGF role of ranibizumab appears to be a factor partly or totally responsible for the development of ranibizumab-induced vitiligo in this case. Observational studies of larger sample size and follow-up duration will contribute to better understanding of systemic effect of intra-vitreal ranibizumab.

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