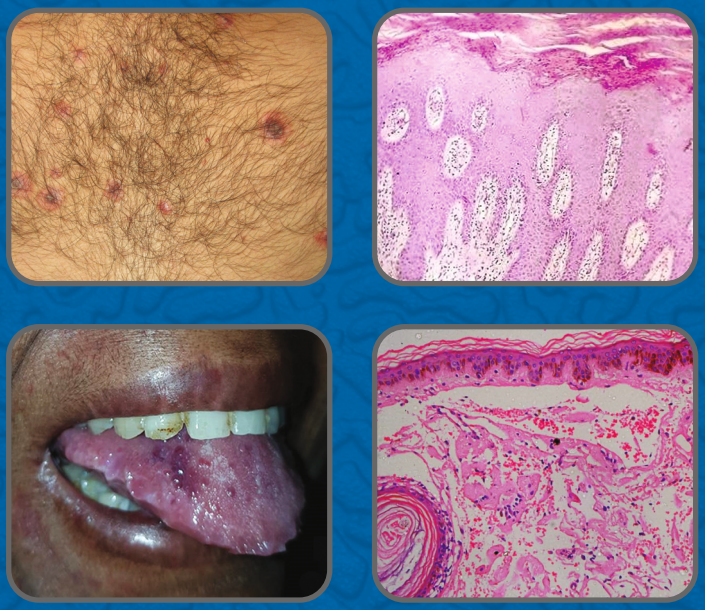
ISSN : 1307-7635

TURKISH JOURNAL OF DERMATOLOGY

VOLUME 14 • ISSUE 3 • JULY-SEPTEMBER 2020

www.tjdonline.org



TURKISH SOCIETY OF DERMATOLOGY 1968

An Official Publication of Turkish Society of Dermatology

Wolters Kluwer

Medknow

Volume No. 14 Issue No. 3 July-September 2020

Turkish Journal of Dermatology

An official publication of Turkish Society of Dermatology

EDITORIAL BOARD

Turkish Journal of Dermatology

An official publication of Turkish Society of Dermatology

General Information

The journal

Turkish Journal of Dermatology (TJOD) (ISSN: Print -1307-7635, Online - 1308-5255) is a peer-reviewed journal published on behalf of Turkish Society of Dermatology. The journal publishes articles related to clinical, epidemiological and research studies about dermatological and venereal diseases, reviews, interesting case reports, presentations like "what is your diagnosis?", articles related to clinical and practical applications, letters to the editor, and editorial reviews. The Journal is published in March, June, September and December.

Information for Authors

There are no page charges for TJOD submissions. Please check http://www.tjdonline.org/contributors.asp for details.

All manuscripts must be submitted online at http://www.journalonweb.com/tjd

Advertising policies

The journal accepts display and classified advertising. Frequency discounts and special positions are available. Inquiries about advertising should be sent to Wolters Kluwer India Private Limited, advertise@medknow.com

The journal reserves the right to reject any advertisement considered unsuitable according to the set policies of the journal.

The appearance of advertising or product information in the various sections in the journal does not constitute an endorsement or approval by the journal and/or its publisher of the quality or value of the said product or of claims made for it by its manufacturer.

Addresses

Editorial Office

Dr. Soner Uzun,
Editor-in-Chief,
Akdeniz University Faculty of Medicine,
Department of Dermatology, Antalya, Turkey
Phone: +902422406710
E-mail: sonuzun@hotmail.com
Website: www.tjdonline.org

Published by

Wolters Kluwer India Private Limited
A-202, 2nd Floor, The Qube, C.T.S. No.1498A/2 Village Marol,
Andheri (East), Mumbai - 400 059, India.
Phone: 91-22-66491818
Website: www.medknow.com; www.wolterskluwer.com

We are glad to share about our planting partnership with "Grow Trees" to reduce carbon emission and help the world to be a greener environment!

Turkish Journal of Dermatology

Volume No. 14 Issue No. 3 July-September 2020

CONTENTS

Turkish Journal of Dermatology on Web

http://www.journalonweb.com/tjd

The Turkish Journal of Dermatology now accepts articles electronically. It is easy, convenient and fast. Check following steps:

1 Registration

- Register from http://www.journalonweb.com/tjd as a new author (Signup as author)
- Two-step self-explanatory process

2 New article submission

- Read instructions on the journal website or download the same from manuscript management site
- Prepare your files (Article file, First page file and Images, Copyright form & Other forms, if any)
- Login as an author
- Click on 'Submit new article' under 'Submissions'
- Follow the steps (guidelines provided while submitting the article)
- On successful submission you will receive an acknowledgement quoting the manuscript ID

3 Tracking the progress

- Login as an author
- The report on the main page gives status of the articles and its due date to move to next phase
- More details can be obtained by clicking on the ManuscriptID
- Comments sent by the editor and reviewer will be available from these pages

4 Submitting a revised article

- Login as an author
- On the main page click on 'Articles for Revision'
- Click on the link "Click here to revise your article" against the required manuscript ID
- Follow the steps (guidelines provided while revising the article)
- Include the reviewers' comments along with the point to point clarifications at the beginning of the revised article file.
- Do not include authors' name in the article file.
- Upload the revised article file against New Article File - Browse, choose your file and then click "Upload" OR Click "Finish"
- On completion of revision process you will be able to check the latest file uploaded from Article Cycle (In Review Articles-> Click on manuscript id -> Latest file will have a number with 'R', for example XXXX_100_15R3.docx)

Facilities

- Submission of new articles with images
- Submission of revised articles
- Checking of proofs
- Track the progress of article until published

Advantages

- Any-time, any-where access
- Faster review
- Cost saving on postage
- No need for hard-copy submission
- Ability to track the progress
- Ease of contacting the journal

Requirements for usage

- Computer and internet connection
- Web-browser (Latest versions - IE, Chrome, Safari, FireFox, Opera)
- Cookies and javascript to be enabled in web-browser

Online submission checklist

- First Page File (rtf/doc/docx file) with title page, covering letter, acknowledgement, etc.
- Article File (rtf/doc/docx file) - text of the article, beginning from Title, Abstract till References (including tables). File size limit 4 MB. Do not include images in this file.
- Images (jpg/jpeg/png/gif/tif/tiff): Submit good quality colour images. Each image should be less than 10 MB) in size
- Upload copyright form in .doc / .docx / .pdf / .jpg / .png / .gif format, duly signed by all authors, during the time mentioned in the instructions.

Help

- Check Frequently Asked Questions (FAQs) on the site
- In case of any difficulty contact the editor

Original Article

Correlation between Psoriasis and ZIP2 and ZIP3 Zinc Transporters

Sevilay Kılıç, Hilal Müserref Şehitoğlu[1]

Departments of Dermatology and [1]Biochemistry, Faculty of Medicine, Canakkale Onsekiz Mart University, Canakkale, Turkey

Abstract

Aims: Psoriasis is a chronic, inflammatory, hyperproliferative skin disease with etiopathogenesis not fully understood. The zinc transporter ZIP2 is associated with keratinocyte differentiation, whereas ZIP3 is associated with T-lymphocyte maturation. In our study, we aimed to show the correlation between psoriasis and ZIP2 and ZIP3 zinc transporters in psoriasis patients. **Subjects and Methods:** The patient group in the study included 60 patients aged with psoriasis vulgaris and a control group of 60 healthy adults. The levels of ZIP2 (SLC39A2) and ZIP3 (SLC39A3) zinc transporters were determined with the ELISA method. Results were compared with control group values and statistically assessed. **Results:** When the ZIP2 and ZIP3 levels are compared in controls and psoriasis patients, the levels were observed to significantly increase compared to controls ($P < 0.05$). When compared to the control group, the results appeared to be statistically significant ($P < 0.05$). **Conclusions:** With etiopathogenesis not fully known, there may be an important relationship between psoriasis development and ZIP2 (SLC39A2) and ZIP3 (SLC39A3) zinc transporters in psoriasis vulgaris patients. This situation may be an important result for understanding how the disease develops and in creating new approaches in terms of treatment for this disease without full cure available.

Keywords: Psoriasis vulgaris, zinc transporters, ZIP2 (SLC39A2), ZIP3 (SLC39A3)

Introduction

Psoriasis is a chronic, systemic, inflammatory, and hyperproliferative skin disease observed at 2%–3% incidence. The most commonly observed clinical type is plaque-type psoriasis (psoriasis vulgaris), and lesions are localized to the scalp, extensor surfaces of the extremities, and sacrogluteal regions, characterized by erythematous squamous plaques with definite margins. Although the etiopathogenesis is still uncertain, it is accepted that cytokines such as interleukin (IL)-17, IL-23, and tumor necrosis factor-alpha (TNF-α) play important roles in the development of psoriasis. The IL-23 and TNF-α produced by inflammatory dendritic cells in the skin induce IL-17 production from Th17 or γδT cells in the skin, and IL-17 is thought to basically affect keratinocytes beginning dermatitis.[1]

Zinc is an important trace element. Severe zinc deficiency is associated with skin diseases and lack of regular operation of the immune system. Most zinc stores in the body are found linked to metalloproteins within cells. Zinc homeostasis is tightly controlled by zinc transporters. Of zinc transporters, ZIP2 is especially associated with keratinocyte differentiation, whereas ZIP3 is associated with T-lymphocyte maturation.[2,3]

In psoriasis patients, studies assessing serum zinc levels have obtained contradictory results. No amelioration is observed in lesions even with zinc supplementation administered to psoriasis patients with low serum zinc levels.[4-6] This situation leads to the consideration that psoriasis pathogenesis may be related not to systemic zinc deficiency but to deficiency at cellular level related to erroneous cutaneous zinc input. The aim of our study, based on literature data, is to assess the levels of zinc transporters providing zinc input into cells, which we consider to have an important role in etiopathogenesis in psoriasis patients and to research the correlation with psoriasis development.

Submission: 08-04-2020 **Revision:** 25-05-2020
Acceptance: 09-06-2020 **Web Publication:** 17-09-2020

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/TJD.TJD_29_20

Address for correspondence: Assoc Prof. Sevilay Kılıç, Department of Dermatology, Faculty of Medicine, Canakkale Onsekiz Mart University, Canakkale, Turkey.
E-mail: sevilay.oguz@gmail.com

How to cite this article: Kiliç S, Şehitoğlu HM. Correlation between psoriasis and ZIP2 and ZIP3 zinc transporters. Turk J Dermatol 2020;14:61-4.

Subjects and Methods

Study design and patients

Our study was permitted by Çanakkale Onsekiz Mart University (ÇOMÜ) Rectorate Clinical Research Ethics Committee on July 11, 2018, number 13-08. It was supported by ÇOMÜ Scientific Research Commission with an independent research project coded THD-2018-2669. Our study group comprised patients attending our clinic from September 2018 to October 2019. The study included 60 psoriasis vulgaris patients aged 18 years and older monitored for at least 2–3-month periods and a control group of 60 healthy adults aged 18 years and older. The control group had no psoriasis lesions on dermatologic examination, had no other systemic disease and/or no systemic medication use, and comprised randomly chosen healthy adults. Before the study, each participant was informed about the aim of the study and written consent was obtained. Blood was centrifuged, and then, serum samples were stored until analysis at −80°C in a freezer.

Laboratory parameters

ZIP2 (SLC39A2) and ZIP3 (SLC39A3) zinc transporter levels were determined with the ELISA method using suitable commercial kits (ZIP2-MBS9331175 and ZIP3-MBS927886; MyBioSource, San Diego, CA, USA). After collecting data, statistical analyses were completed and significance analysis was performed for the control and study groups.

The ZIP2 and ZIP3 analyses were completed with the quantitative sandwich ELISA method. Microplate, standards, and samples were brought to room temperature (18°C–25°C). The blind well had no chemical added. After standards and samples were pipetted into the wells, horseradish peroxidase-conjugated reagent was added and was incubated at 37°C for 60 min. All wells were washed four times. Then, each well had chromogen A and B solutions added and was incubated at 37°C for 15 min, and then, the reaction was stopped with stop solution. Optical intensity was measured at 450 nm within 15 min of adding the stop solution. Based on the graphs obtained from standards, concentrations of samples were determined.

Statistical analysis

Statistical analysis of ZIP2 and ZIP3 levels in the psoriasis and control groups was completed using the IBM SPSS statistics 21.0 program (Chicago, IL, USA). Statistical significance was accepted as $P < 0.05$. Differences between groups were determined with the Kolmogorov-Smirnov ($P < 0.05$) and nonparametric Mann–Whitney U-test for ZIP2 ($P = 0.000$). For ZIP3, groups had normal distribution according to the Kolmogorov-Smirnov test ($P > 0.05$), so the independent *t*-test was applied ($P < 0.05$). Correlations between demographic data and ZIP2 and ZIP3 values were determined with the Pearson and Spearman correlation tests. Results are expressed as mean ± standard deviation.

Results

When the ZIP2 levels are compared in controls and psoriasis patients, they appear to increase by significant levels compared to controls ($P < 0.05$) [Figure 1 and Table 1]. At the same time, the ZIP3 levels were increased in psoriasis, similar to ZIP2 [Figure 1 and Table 1]. When assessed compared to the control group, the results are statistically significant ($P < 0.05$).

Discussion

Zinc is categorized as a trace element comprising <0.005% of total body weight. In circulation, it is found at concentrations of 70–120 mcg/dL, with 60% linked to albumin and 30% linked to macroglobulin. Primary zinc stores are the liver and kidneys. However, body zinc stores are found linked to metalloproteins in most cells. It is a natural metal compound or activating cofactor for more than 70 important enzyme systems, led by alkaline phosphatase. It plays a role in regulation of nucleoproteins and inflammatory cell activation.[7]

Zinc is very important for the immune system. Phagocytic function disorder resulting from zinc deficiency is associated with lymphocyte reduction, reduced immunoglobulin production, reduced T4/T8 ratio, and reduced IL-2 production.[8] The interaction between T-lymphocytes and IL-2 is important for both tolerance and immune response. When literature data are investigated, increases in IL-2 appear to be associated with a reduction in psoriasis severity and an increase in quality of life.[9,10] The role of IL-2 in psoriasis is to ensure differentiation of regulatory T-cells from immature T-cells and to ease differentiation of infector and memory cells in T-cells exposed to antigens. In addition, it is debatable whether the reduction in IL-2 levels is associated with psoriasis development or not.[11,12]

ZIP2 is a zinc transporter found in cell membranes and plays a role in zinc intake into cells. It is found at higher levels in the epidermis than the dermis. In psoriasis, epidermal turnover is shorter by eight times compared to normal and keratinocyte differentiation remains insufficient. ZIP2 is required for both proliferation and terminal differentiation of keratinocytes in epidermal turnover, and a study showed ZIP2 levels increased in parallel with differentiation.[2,13] Keratinocytes increase ZIP 2 expression when extracellular zinc levels are reduced, thereby maintaining homeostasis and preserving the ability to differentiate. A similar phenomenon was observed in a study using monocytic cells.[14] Another study observed vesiculobullous lesions formed on the skin during early embryogenesis in ZIP2 knockout mice,[15] and although the underlying mechanism is not fully known, this situation is probably due to abnormal differentiation of keratinocytes.

ZIP3 is expressed at high rates by CD34+ human hematopoietic stem cells, and a study of mice showed a correlation between ZIP3

Table 1: Comparison of ZIP2 and ZIP3 levels in the psoriasis and control groups

	ZIP2	ZIP3
Control	1.69±1.42*	109.61±70.88*
Psoriasis	8.39±5.51[b]	965.06±698.54[b]

Results shown with [b]are seen to be statistically significant when compared with those marked *$P<0.05$

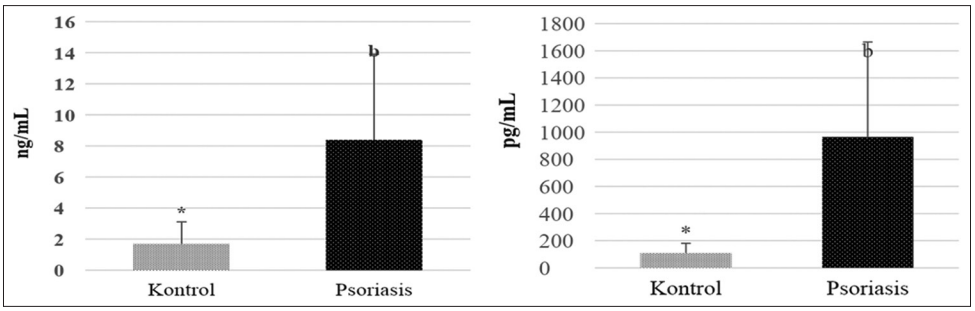


Figure 1: ZIP2 (SLC39A2) and ZIP3 (SLC39A3) zinc transporter levels in psoriasis patients

and T-cell maturation.[3] Psoriasis is a T-lymphocyte-mediated disease and is thought to occur as a result of complex mechanisms between T-lymphocytes with dendritic cells, macrophages, mast cells, neutrophils, and keratinocytes.

Cutaneous changes are frequently observed in patients with zinc deficiency. Acrodermatitis enteropathica is a rare disease forming as a result of a hereditary partial defect in intestinal zinc absorption with recessive transition. The disease was identified to cause mutation in the gene for the zinc transporter protein ZIP4 (SLC39A4).[16] In affected infants, as a result of zinc deficiency, there is skin involvement with appearance of erythematous and vesiculobullous lesions and alopecia with clinical findings affecting other systems such as growth development retardation, delayed sexual maturation, neuropsychiatric symptoms, and frequent infections. The syndrome responds to oral zinc supplementation.

When studies about the serum zinc levels in psoriasis patients are investigated, there are contradictory results reported. Some researchers have found low serum zinc levels in psoriasis patients compared to the control group,[17,18] whereas some have not found such a difference.[19,20] In psoriasis patients, a study comparing epidermal and serum zinc levels found that epidermal and serum zinc levels were not correlated; however, epidermal zinc values were lower in psoriasis patients.[21] This result shows that patients with reduced epidermal zinc concentrations may have zinc deficiency even if they have normal serum zinc values. In addition, in psoriasis patients, even with low serum zinc concentrations, oral zinc supplements remain as effective as placebo.[5] As a result, in relation to psoriasis development, it may be considered a defect of subcellular zinc metabolism caused by erroneous zinc input into the skin rather than systemic zinc deficiency. In our study, we found that ZIP2 and ZIP3 levels were higher in our psoriasis patients independent of disease severity. This situation leads us to consider it may form as a result of complicated correlations between disrupted zinc homeostasis, increased keratinocyte proliferation, and chronic inflammatory cell infiltration.

Conclusions

For immune-mediated diseases such as psoriasis, there is still no treatment method providing full cure or no laboratory test assessing disease severity or treatment efficacy.[22] In addition, the effect of the most effective treatments sometimes reduces due to changes in cytokine profile and may even become ineffective. In conclusion, the increase in ZIP2 and ZIP3 levels obtained in our psoriasis patients may be a marker of a zinc deficiency at cellular level in accordance with roles in pathogenesis. Zinc deficiency at cellular level affects the cytokine profile, and we think that zinc deficiency at the cellular level affects the cytokine profile. This may be important in the pathogenesis of psoriasis lesions. It may even explain why psoriasis patients have different treatment responses to similar treatments.

The importance of the zinc carrier family is emphasized by the numerous functions of these proteins in many disease states. Irregularity of zinc transporters causes dissociation in intracellular zinc levels. this situation have profound effects on metabolic homeostasis, which affects multiple signaling pathways associated with normal development, growth, differentiation, and death. Zinc carriers are essential for the control of intracellular zinc. Mechanisms that disrupt this process may contribute to the development of psoriasis, one of the inflammatory and chronic inflammatory diseases. Targeting these zinc carriers in psoriasis therapy can lead to the development of new treatment options.[23]

In light of our data, we think that zinc transporters may be assessed as a part of treatment of psoriasis patients, perhaps to optimize treatments.

Acknowledgments

This research was supported by funds from the Çanakkale Onsekiz Mart University. This project has been funded in whole with the Çanakkale Onsekiz Mart University The Scientific Research Coordination Unit, Project number: THD-2018-2669".

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Hawkes JE, Chan TC, Krueger JG. Psoriasis pathogenesis and the development of novel targeted immune therapies. J Allergy Clin Immunol 2017;140:645-53.

2. Rezaei KA, Chen Y, Cai J, Sternberg P. Modulation of Nrf2-dependent antioxidant functions in the RPE by Zip2, a zinc transporter protein. Invest Ophthalmol Vis Sci 2008;49:1665-70.
3. Dufner-Beattie J, Huang ZL, Geiser J, Xu W, Andrews GK. Generation and characterization of mice lacking the zinc uptake transporter ZIP3. Mol Cell Biol 2005;25:5607-15.
4. Verma S, Thakur BK. Dramatic response to oral zinc in a case of subacute form of generalized pustular psoriasis. Indian J Dermatol 2012;57:323-4.
5. Voorhees JJ, Chakrabarti SG, Botero F, Miedler L, Harrell ER. Zinc therapy and distribution in psoriasis. Arch Dermatol 1969;100:669-73.
6. Lei L, Su J, Chen J, Chen W, Chen X, Peng C. Abnormal serum copper and zinc levels in patients with psoriasis: A meta-analysis. Indian J Dermatol 2019;64:224-30.
7. Beyersmann D, Haase H. Functions of zinc in signaling, proliferation and differentiation of mammalian cells. Biometals 2001;14:331-41.
8. Prasad AS. Zinc and immunity. Mol Cell Biochem 1998;188:63-9.
9. Khandpur S, Gupta V, Das D, Sharma A. Is there a correlation of serum and tissue T helper-1 and -2 cytokine profiles with psoriasis activity and severity? A cross-sectional study. Indian J Dermatol Venereol Leprol 2018;84:414-8.
10. Solberg SM, Sandvik LF, Eidsheim M, Jonsson R, Bryceson YT, Appel S. Serum cytokine measurements and biological therapy of psoriasis – Prospects for personalized treatment? Scand J Immunol 2018;88:e12725.
11. Adler G, Skonieczna-Żydecka K, Madlani A, Ogonowski J, Grochans E, Pierzak-Sominka J, *et al*. Association between depression, parameters of adiposity and genetic polymorphisms of pro-inflammatory cytokines: IL-1α, IL-1β, IL-2 and IL-6 in subjects over 55 years old. Acta Biochim Pol 2016;63:253-9.
12. Tucker P, Pfefferbaum B, Nitiéma P, Khan Q, Aggarwal R, Walling EE. Possible link of Interleukin-6 and Interleukin-2 with psychiatric diagnosis, ethnicity, disaster or BMI. Cytokine 2017;96:247-52.
13. Inoue Y, Hasegawa S, Ban S, Yamada T, Date Y, Mizutani H, *et al*. ZIP2 protein, a zinc transporter, is associated with keratinocyte differentiation. J Biol Chem 2014;289:21451-62.
14. Cao J, Bobo JA, Liuzzi JP, Cousins RJ. Effects of intracellular zinc depletion on metallothionein and ZIP2 transporter expression and apoptosis. J Leukoc Biol 2001;70:559-66.
15. Peters JL, Dufner-Beattie J, Xu W, Geiser J, Lahner B, Salt DE, *et al*. Targeting of the mouse Slc39a2 (Zip2) gene reveals highly cell-specific patterns of expression, and unique functions in zinc, iron, and calcium homeostasis. Genesis 2007;45:339-52.
16. Küry S, Dréno B, Bézieau S, Giraudet S, Kharfi M, Kamoun R, *et al*. Identification of SLC39A4, a gene involved in acrodermatitis enteropathica. Nat Genet 2002;31:239-40.
17. Morgan ME, Hughes MA, McMillan EM, King I, Mackie RM. Plasma zinc in psoriatic inpatients treated with local zinc application. Br J Dermatol 1980;102:579-83.
18. Greaves M, Boyde TR. Plasma-zinc concentrations in patients with psoriasis, other dermatoses, and venous leg ulceration. Lancet 1967;2:1019-20.
19. Molokhıa MM, Portnoy B. Neutron activation analysis of trace elements in skin V. Copper and zinc in psoriasis. Br J Dermatol 1970;83:376-81.
20. Hinks LJ, Young S, Clayton B. Trace element status in eczema and psoriasis. Clin Exp Dermatol 1987;12:93-7.
21. Michaëlsson G, Ljunghall K. Patients with dermatitis herpetiformis, acne, psoriasis and Darier's disease have low epidermal zinc concentrations. Acta Derm Venereol 1990;70:304-8.
22. Ergun T. Systemic treatment of psoriasis: Rational use of therapeutics and controversial issues. Review. Turk J Dermatol 2007;1:8-14.
23. Adulcikas J, Sonda S, Norouzi S, Sohal SS, Myers S. Targeting the zinc transporter ZIP7 in the treatment of insulin resistance and type 2 diabetes. Nutrients 2019;11:408.

Original Article

Hepatitis B Virus Reactivation in Patients with Psoriasis on Biologic Therapies: A Retrospective Study

Sinan Özçelik, Fatma Arzu Kılıç

Department of Dermatology, Balıkesir University, Faculty of Medicine, Balikesir, Turkey

Abstract

Background: There are limited data on the safety of biological therapies in psoriasis patients with hepatitis B virus (HBV) infection in the literature, and are still ongoing controversies about HBV reactivation in patients treated with biologics for psoriasis. **Aims:** This was aimed to investigate the demographic, clinical, and laboratory characteristics of the patients with HBV seropositive receiving biological treatment for psoriasis. **Study Design:** This was a retrospective observational study. **Materials and Methods:** Ninety-seven patients with psoriasis treated with biologics in the outpatient clinic were evaluated retrospectively. Of these, 16 patients with HBV seropositive were included in the study. Patients with positive HBV serology were divided into three groups as chronic HBV infection, past HBV infection, and isolated core antibody positivity (HBV core-specific antibody [HBcAb]). The demographic, clinical, and laboratory characteristics of the patients were obtained from the records. **Results:** Of the patients, 5 patients were female (31.2%), and 11 were male (68.8%). The mean age of the patients was 55.81 ± 11.05. Thirteen of the patients had past HBV infection, three had isolated HBcAb positive. Infliximab (n = 13) was the most common biologic agent used, followed by adalimumab (n = 6), secukinumab (n = 4), ustekinumab (n = 2), and etanercept (n = 2). The mean duration of treatment was 3.59 ± 2.76 years. The HBV reactivation occurred in only one patient with past HBV infection receiving infliximab (6.2%). **Conclusion:** It remains unclear how exactly the biologic drugs for psoriasis impact viral reactivation. For the safe use of biological agents in psoriasis patients with HBV seropositive, screening tests must be performed with a triple serology, including HBV surface antigen, HBV surface-specific antibody, and HBcAb. The patients who have positive HBV serology must be monitored closely with reactivation markers and receive antiviral prophylaxis if they are at moderate-to-high risk of HBV reactivation.

Keywords: Biologic agent, hepatitis B virus, psoriasis, reactivation

Introduction

In recent years, biological therapies play an important role in the treatment of moderate-to-severe psoriasis. It is said that biologics that target specific parts of the immune system that play a crucial role in the pathogenesis of psoriasis are usually well tolerated and have few side effects. However, biologics can cause reactivation of some infections, such as hepatitis B virus (HBV), through their immunomodulatory activity. At this point, there are very limited data on the safety of biological therapies in psoriasis patients with HBV infection in the literature and are still ongoing controversies about HBV reactivation in patients treated with biologics for psoriasis. Besides the limited data on the management of biologics in patients with HBV infection, most of these data have been obtained from studies with diseases other than psoriasis (e.g., rheumatological, gastroenterological).[1-3] In addition to these, there are many difficulties to find HBV reactivation rates in the real-world. For these reasons, we aimed to investigate the demographic, clinical, and laboratory characteristics of the patients with HBV seropositive receiving biological treatment for psoriasis with this study.

Materials and Methods

All patients with psoriasis who are treated with biologics reached to the outpatient clinic were evaluated retrospectively.

Submission: 29-04-2020 **Revision:** 19-05-2020
Acceptance: 09-06-2020 **Web Publication:** 17-09-2020

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/TJD.TJD_42_20

Address for correspondence: Dr. Sinan Özçelik, Department of Dermatology, Balıkesir University, Faculty of Medicine, Balikesir, Turkey.
E-mail: sinozc@gmail.com

How to cite this article: Özçelik S, Kılıç FA. Hepatitis B virus reactivation in patients with psoriasis on biologic therapies: A retrospective study. Turk J Dermatol 2020;14:65-70.

A total of 97 patients with psoriasis were receiving biological therapy between August 2014 and September 2019. Of these, only HBV seropositive patients were included in the study. HBV status has been classified according to the European Association for the Study of Liver Disease:

1. Chronic HBV infection (HBV surface antigen [HBsAg]-positive)
2. Past HBV infection (HBsAg-negative, HBV surface-specific antibody [HBsAb]-positive, and HBV core-specific antibody [HBcAb]-positive)
3. Isolated core antibody positivity (HBsAg negative, HBsAb negative, and HBcAb positive).[4]

Demographic variables, medical history, type of psoriasis, previous or concomitant immunosuppressive therapies, use of antiviral prophylaxis, type and duration of biological therapy (adalimumab, etanercept, infliximab, ustekinumab, secukinumab) were recorded retrospectively from the patients' medical records. Laboratory data (HBsAg, HBsAb, HBcAb, HBV DNA, alanine aminotransferase, aspartate transaminase) was also extracted from the records to determine serologic status at baseline and during treatment at various intervals. We included all patients whose viral load was assessed at the beginning of biological therapy and in every 3 months during treatment.

The American Association for the Study of Liver Diseases (AASLD)-recommended criteria for HBV reactivation were considered.[5] According to AASLD, HBV reactivation in HBsAg-positive, anti-HBc–positive patients is reasonably defined as one of the following:

1. A 2 log (100-fold) increase in HBV DNA compared to the baseline level
2. HBV DNA 3 log (1000) IU/mL in a patient with previously undetectable level (given that HBV-DNA levels fluctuate)
3. HBV DNA 4 log (10,000) IU/mL if the baseline level is not available.

For HBsAg-negative, anti-HBc–positive patients, the following criteria are reasonable for HBV reactivation:

1. HBV DNA is detectable or
2. Reverse HBsAg seroconversion occurs (reappearance of HBsAg).[5]

Approval for the study was obtained from the local ethics committee (Decision number 2019/92; 08/07/2019). Statistical analyses were conducted using STATA (version 13, StataCorp LLC College Station, Texas, USA) program. Data obtained by counting are expressed as numbers and percentages.

Results

A total of 97 patients with psoriasis receiving biological therapy were examined retrospectively, and 16 of them were included in the study. Five of all patients were female (31.2%) and eleven were male (68.8%). The mean age of the patients was 55.81 ± 11.05. The mean age of females was 62.2 ± 7.79, and 52.9 ± 11.37 for the male.

All patients had plaque-type psoriasis (mean duration of 21.31 years, range 6–45 years). The demographic, clinical, and laboratory characteristics of patients are shown in Tables 1 and 2.

Thirteen of the patients had past HBV infection, three had isolated HBcAb positive. No patient had chronic HBV infection and detectable serum HBV DNA at baseline. Out of 13 patients, only three patients with past HBV infection were receiving antiviral prophylaxis with *tenofovir* that were suggested by gastroenterologists [Table 2].

Table 1: Clinical characteristics of cases at baseline

Case	Age	Sex	Medical history	Psoriasis duration (years)	HBV status	Previous immunotherapy	Biologic therapies	Biological treatment duration (years)
1	40	Male	-	29	Isolated	MTX, CYS	INF	1
2	45	Male	-	15	Past	MTX, CYS	SEC	1
3	53	Female	HT	36	Past	MTX, CYS	INF, ETA, ADA*	10
4	34	Male	-	13	Past	MTX, CYS	ETA, INF, ADA, UST, SEC*	10
5	58	Male	-	45	Past	MTX, CYS	INF, ADA*	4
6	58	Male	DYS	12	Isolated	MTX	INF, SEC*	2
7	50	Male	-	11	Past	MTX	INF	3
8	65	Male	-	19	Past	MTX	INF	3
9	58	Female	DM, HT	30	Past	MTX	ADA, INF*	4
10	63	Female	-	25	Past	MTX, CYS	INF	2
11	66	Male	-	19	Isolated	MTX, CYS	INF, SEC*	4
12	68	Male	-	14	Past	MTX, CYS	INF	1
13	55	Male	-	34	Past	MTX, CYS	ADA	4
14	74	Female	HT	15	Past	MTX	INF, ADA*	4.5
15	43	Male	DM	18	Past	MTX, CYS	UST	2
16	63	Female	-	6	Past	MTX	INF	2

*Currently used biologics. ADA: Adalimumab, CYS: Cyclosporine, DM: Diabetes mellitus, DYS: Dyslipidemia, ETA: Etanercept, HBV: Hepatitis B virus, HT: Hypertension, INF: Infliximab, MTX: Methotrexate, PASI: Psoriasis Area and Severity Index, SEC: Secukinumab, UST: Ustekinumab

Table 2: Laboratory characteristics of cases at baseline

Case	HBsAg	HBsAb* (mIU/mL) Baseline	HBsAb (mIU/mL) Follow up	HBcAb	Viral load (IU/mL) Baseline	Viral load (IU/mL) End	ALT (IU/L) Baseline	ALT (IU/L) End	AST (IU/L) Baseline	AST (IU/L) End	Antiviral PRX
1	Negative	0.83	10	Positive	<10	<10	40	30	24	25	-
2	Negative	12.64	16.86	Positive	<10	<10	26	28	37	25	-
3	Negative	160.39	151.63	Positive	<10	<10	19	17	17	17	-
4	Negative	672.02	1000	Positive	<10	<10	51	67	28	40	-
5	Negative	39.92	202.57	Positive	<10	<10	20	28	22	24	-
6	Negative	0.43	5.53	Positive	<10	<10	13	35	25	75	-
7	Negative	202.59	287.69	Positive	<10	<10	32	35	25	27	-
8	Negative	186.39	173.8	Positive	<10	<10	11	15	16	19	+
9	Negative	504.36	1000	Positive	<10	<10	19	11	12	11	+
10	Negative	130.17	184.25	Positive	<10	<10	22	10	22	21	-
11	Negative	6.34	4.78	Positive	<10	<10	10	14	32	27	-
12	Negative	16.53	15.83	Positive	<10	<10	14	13	16	14	-
13	Negative	1000	1000	Positive	<10	<10	26	16	29	22	-
14	Negative	53.14	39.98	Positive	<10	<10	39	46	26	36	-
15	Negative	101.6	111.63	Positive	<10	<10	37	27	18	21	+
16	Negative	64.89	47.49	Positive	<10	52000	16	32	18	26	-

*HBsAb levels above 10 IU/mL were considered positive. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HBV: Hepatitis B virüs, HBcAb: HBV core antibody, HBsAb: HBV surface antibody, PRX: Prophylaxis

All the patients had the use of conventional drug at least, such as methotrexate and cyclosporine, before biological treatment. Infliximab (n = 13) was the most common biologic agent used, followed by adalimumab (n = 6), secukinumab (n = 4), ustekinumab (n = 2), and etanercept (n = 2). While nine patients had the use of only one biological agent, seven had a history of more than one biological agent used. The mean duration of biological treatment was 3.59 ± 2.76 years (range 1–10). The mean duration of treatment was 2 years for infliximab, 1.7 years for etanercept, 3.1 years for adalimumab, 2.5 years for ustekinumab, and 1.7 years for secukinumab.

The HBV reactivation occurred in only one patient with past HBV infection who did not receive antiviral prophylaxis. The patient developed detectable HBV DNA without reverse seroconversion to HBsAg positive. Her serum HBV DNA was measured as 52000 IU/mL [Table 2]. As soon as noticing the reactivation, the drug discontinued, and she was referred to the gastroenterologist. The reactivation rate was 6.2% among all patients, and 7.6% among the patients who did not receive antiviral prophylaxis. Three patients who were receiving antiviral prophylaxis did not develop reactivation during follow-up.

Discussion

Biological therapies have been playing an important role in the treatment of moderate-to-severe psoriasis in recent years. Biologic drugs can cause HBV reactivation due to their immunomodulatory effects. HBV infection is one of the most common infectious liver diseases in the World. There are >292 million carriers of HBV worldwide. In Turkey, the estimated number of HBV carriers is 3.3 million.[6]

Once the HBV enters the nucleus of the host hepatocytes, the viral DNA is transformed into a covalently closed circular DNA, which serves as a template for viral replication throughout the host's lifetime. Reactivation of HBV infection is characterized by an abrupt increase in HBV replication. Patients with seropositive HBV infection who receive immunosuppressive therapy are at risk for HBV reactivation. Reactivation most commonly occurs in patients with HBsAg (especially chronic active carriers). It can also rarely occur in patients with past or occult infections.[7]

As can be understood, the risk of HBV reactivation in patients receiving immunosuppressive treatment is higher in patients with HBsAg positive than negatives. American Gastroenterological Association (AGA) defined risk levels for HBV reactivation in patients receiving immunosuppressive agents.[8] The risk for HBV reactivation is categorized into high risk (>10%), moderate risk (1%–10%), and low risk (<1%) depending upon the serological status and the type of immunosuppressive therapy.[9] According to this classification of AGA, the reactivation rates in patients with HBsAg-negative and HBcAg-positive receiving biologic drugs vary between medium and low risk (1%–10%).[8] However, it may be said that the risk of reactivation is very low in patients with HBsAg-negative and HBcAb-positive, receiving biologics for psoriasis.[9] The probable reason for this is that while biologic drugs are generally used in combination with other immunosuppressive treatments in rheumatological, gastroenterological diseases, are usually used alone in dermatological diseases.

There are limited data on the safety of biologic drugs in psoriasis patients with HBV infection in the literature. Current guidelines do not recommend the use of biological

drugs in patients with active HBV infection due to the risk of reactivation.[10-12] However, prior or current HBV infection is not necessarily an absolute contraindication to biological treatment for the treatment of psoriasis. Psoriasis patients with HBV infection may receive biologic drugs, but they should be evaluated carefully, closely monitored for signs of reactivation, and managed in conjunction with a gastroenterologist.[9] Available data on the management and treatment of psoriasis with biologics in patients with HBV infection are based on few prospective studies, some retrospective studies, lots of case series, and reports in the literature.[13] Table 3 shows the findings of various studies investigating reactivation in psoriasis patients with positive HBV serology receiving biological therapy.

In this study, the psoriasis patients who have past HBV infection or isolated HBcAb positivity were at low risk for reactivation with biologics. However, HBV reactivation occurred in only one patient who was taking infliximab, and also had past HBV infection. This patient had also taken methotrexate for a long time. The use of prior immunosuppressive therapy may have also impacted the risk of reactivation in the patient. In 2011, a review published by Pérez-Alvarez *et al*. analyzing 257 cases reported the risk of reactivation is 5% in 168 HBcAb positive patients treated with anti-tumor necrosis factor (TNF) agents.[14] A systematic review including 175 patients with HBcAb positive treated with biologic drugs reported a reactivation rate of 1.14%.[15] Another systematic review involving 712 rheumatic patients with past HBV infection treated with biologic drugs found that the reactivation rate was 1.7%.[16] A recent study in Turkey, including 29 patients with past HBV infection or isolated HBcAb positivity treated with biologic drugs, found that five of all patients (4 had psoriasis, one had rheumatoid arthritis) developed HBV reactivation.[17] It is intriguing that a very high reactivation rate of 17.2% was found for a low-risk group in this study. It is seen that there are several studies showing the HBV reactivation rates in patients receiving biologic drugs are quite variable [Table 3]. This is because both these studies and ours had a low number of cases. Hence, there is a strong need for larger studies on this issue.

All patients had HBcAb positive in this study, and been consulted to gastroenterologists for the requirement of antiviral prophylaxis before treatment with biologic drugs. Despite there were 10 patients with past HBV infection, only 3 of them were initiated antiviral prophylaxis by gastroenterologists before biological treatment. Although all the patients in this study were at low risk for HBV reactivation with biologics, while antiviral prophylaxis was recommended in some patients, and were not recommended in some patients. Unfortunately, no guidelines exist for this particular issue with clear suggestions. It seems that while some gastroenterologists prefer antiviral prophylaxis over monitoring for patients with HBcAb positive receiving biologic drugs, some prefer monitoring over antiviral prophylaxis. It is understood that the decision to administer antiviral prophylaxis for patients with HBcAb positive depends on the physician's discretion, unless the risk of HBV reactivation in patients with HBsAg negative and HBcAb

Table 3: Summary of reports and studies describing hepatitis B virüs reactivation in patients psoriasis on biologic therapies

Study	Disease, *n*	HBsAg+ (inactive carriers), *n*	HBcAb+ HBsAb± (past or isolated), *n*	Biologic therapies (mostly used)	Prophylaxis, *n*	Reactivation, *n* (%)*
Charpin *et al*., 2009[18]	PsA, 5	0	5	ETA	0	0
Prestinari *et al*., 2010[19]	PsO, 1	0	1	ETA	0	0
Nosotti *et al*., 2010[20]	PsO, 4; PsA, 3	1	6	ETA	1	0
Caporali *et al*., 2010[21]	PsA, 4	0	4	INF	0	0
Kim *et al*., 2010[3]	PsA, 2	0	2	ETA	0	0
Fotiadou *et al*., 2011[22]	PsO, 7	7	0	ADA, ETA	7	0
Prignano *et al*., 2011[23]	PsO, 12	0	12	ETA	0	0
Cassano *et al*., 2011[24]	PsO, 28; PsA, 34	0	62	ETA	0	0
Cho *et al*., 2012[25]	PsO, 7	7	0	ETA	1	0
Koskinas *et al*., 2013[26]	PsO, 1	0	1	UST	0	1
Laurenti *et al*., 2013[27]	PsA, 8	1	7	ADA	1	0
Navarro *et al*., 2013[28]	PsO, 5	5	0	ETA	5	0
Notarnicola *et al*., 2014[29]	PsA, 1	0	1	INF	0	1
Navarro *et al*., 2014[30]	PsO, 13	0	13	ETA	0	0
Sanz-Bueno *et al*., 2015[31]	PsO, 20	0	20	ETA, ADA	0	0
Snast *et al*., 2017[15]	PsO, 26	1	25	ETA	2	0
Solay *et al*., 2018[17]	PsO, 23	0	23	ADA	3	4 (17.3%)
Ting *et al*., 2018[13]	PsO, 54	10	44	UST	2	3 (5.6%)
Chiu *et al*., 2018[32]	PsO, 49	25	24	SEC	3	7 (14.2%)
This study	PsO, 16	0	16	INF	3	1 (6.2%)

*Percentage values are for studies only. ADA: Adalimumab, ETA: Etanercept, INF: Infliximab, SEC: Secukinumab, UST: Ustekinumab, PsO: Psoriasis, PsA: Psoriatic arthritis, HBV: Hepatitis B virüs, HBcAb: HBV core antibody, HBsAb: HBV surface antibody, HBsAg: HBV surface antigen

positive receiving biologic drugs is entirely clear. Besides the physician's discretion, comorbidity status of patients, and the resources made available by the healthcare system may also impact this decision.[9]

Out of the 16 patients, 13 had HBsAb positive and 3 had HBsAb negative (isolated HbcAb positive) in this study. HBV reactivation occurred in the patient who had both HBcAb and HBsAb positive. While some evidence concerning the risk for HBV reactivation suggests that patients who are HBsAb negative are at slightly higher risk compared with those who are HBsAb positive, several studies suggest that there are limited data on this issue.[33] Therefore, it is not clear whether the risk of HBV reactivation in patients with HBcAb positive receiving biologic drugs varies depending on the HBsAb status.

Most cases of HBV reactivation in patients treated with biologic drugs reported in the literature, occurred in those using infliximab for rheumatological and dermatological diseases.[9] Infliximab ($n = 13$) was the most common biologic agent used, and also found the responsible drug for the reactivation in the patient with past HBV infection in this study. However, there are also various studies reporting that etanercept or adalimumab also were reported as responsible drugs for the reactivation in patients [Table 3]. As a class, TNF-alpha inhibitors have been considered to be associated with a relatively high incidence of HBV reactivation compared to other biologics. There may be two possible explanations for this. The first is that reactivation of HBV in patients receiving TNF inhibitors may be related to a suppressive effect of endogenous TNF-alpha on the replication of HBV. The second is that TNF inhibitors are one of the first biologic drugs that enter the pharmaceutical market. For the second reason, more experience and reports on side effects of TNF inhibitors are expected than interleukin (IL) inhibitors. Although the risk of HBV infection reactivation appears to be low for IL inhibitors (ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab), there are several studies reporting that HBV reactivation occurred in patients with HBV using ustekinumab and secukinumab for psoriasis published in the literature.[13,32] However, it can be said that there is not an increase in HBV reactivation rates based on long-term data on ustekinumab.[15] Clinical data on the effect of IL-17 inhibitors (secukinumab, ixekizumab, brodalumab) on HBV reactivation are limited to case reports. A recent study investigating the risk of reactivation of HBV or HCV in psoriasis patients receiving secukinumab reported that seven of all patients (7/49) developed HBV reactivation.[32] The effects of IL-23 inhibitors (guselkumab, tildrakizumab, risankizumab) on psoriasis patients with HBV are unclear because of excluding patients with HBV from phase trials. However, based on their mechanism of action, IL-17 and IL-23 inhibitors theoretically may not significantly increase the risk of HBV reactivation. Since the risk for reactivation of HBV infection appears to be low for IL-17 and IL-23 inhibitors, these drugs seem to be the preferred biologic agents for psoriasis patients with HBV infection for now.

This study has several limitations. The first one is its retrospective nature. The second one is that the study includes low number of cases. Another one is that the patients who were consulted to the gastroenterologists for the requirement of antiviral prophylaxis, were examined by different gastroenterologists.

Conclusion

On the basis of the available evidence, it remains unclear how exactly the biologic drugs for psoriasis impact viral reactivation. Therefore, it is very important to define the safety profile of biologic drugs in psoriasis patients with positive HBV serology. Although patients who are HBsAg positive are at higher risk for HBV reactivation, patients who are HBsAg negative and HbcAb positive are also at low risk. Therefore, triple serology testing with HBsAg, HBsAb, and HBcAb must be done to identify HBV status before treatment with biologic drugs. The patients who have positive HBV serology must be monitored closely and receive antiviral prophylaxis if they are at moderate to high risk of HBV reactivation. In conclusion, because each patient and its disease have their own characteristics, every patient should be carefully evaluated for the risk: benefit ratio of biologic therapy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Domm S, Cinatl J, Mrowietz U. The impact of treatment with tumour necrosis factor-alpha antagonists on the course of chronic viral infections: A review of the literature. Br J Dermatol 2008;159:1217-28.
2. Viganò M, Degasperi E, Aghemo A, Lampertico P, Colombo M. Anti-TNF drugs in patients with hepatitis B or C virus infection: Safety and clinical management. Expert Opin Biol Ther 2012;12:193-207.
3. Kim YJ, Bae SC, Sung YK, Kim TH, Jun JB, Yoo DH, *et al*. Possible reactivation of potential hepatitis B virus occult infection by tumor necrosis factor-alpha blocker in the treatment of rheumatic diseases. J Rheumatol 2010;37:346-50.
4. European Association for the Study of the Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012;57:167-85.
5. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, *et al*. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology (Baltimore, Md) 2018;67:1560-99.
6. Özkan H. Epidemiology of chronic hepatitis B in Turkey. Euroasian J Hepatogastroenterol 2018;8:73-4.
7. European Association for the Study of the Liver Electronic address: Easloffice@easlofficeeu, European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370-98.
8. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT, American Gastroenterological Association Institute. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015;148:215-9.
9. Piaserico S, Messina F, Russo FP. Managing psoriasis in patients with HBV or HCV ınfection: Practical considerations. Am J Clin Dermatol

2019;20:829-45.
10. Menter A, Strober BE, Kaplan DH, Kivelevitch D, Prater EF, Stoff B, *et al*. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. J Am Acad Dermatol 2019;80:1029-72.
11. Gisondi P, Altomare G, Ayala F, Bardazzi F, Bianchi L, Chiricozzi A, *et al*. Italian guidelines on the systemic treatments of moderate-to-severe plaque psoriasis. J Eur Acad Dermatol Venereol 2017;31:774-90.
12. Smith CH, Jabbar-Lopez ZK, Yiu ZZ, Bale T, Burden AD, Coates LC, *et al*. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. Br J Dermatol 2017;177:628-36.
13. Ting SW, Chen YC, Huang YH. Risk of hepatitis B reactivation in patients with psoriasis on ustekinumab. Clin Drug Investig 2018;38:873-80.
14. Pérez-Alvarez R, Díaz-Lagares C, García-Hernández F, Lopez-Roses L, Brito-Zerón P, Pérez-de-Lis M, *et al*. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: Analysis of 257 cases. Medicine (Baltimore) 2011;90:359-71.
15. Snast I, Atzmony L, Braun M, Hodak E, Pavlovsky L. Risk for hepatitis B and C virus reactivation in patients with psoriasis on biologic therapies: A retrospective cohort study and systematic review of the literature. J Am Acad Dermatol 2017;77:88-97.e5.
16. Mori S, Fujiyama S. Hepatitis B virus reactivation associated with antirheumatic therapy: Risk and prophylaxis recommendations. World J Gastroenterol 2015;21:10274-89.
17. Solay AH, Acar A, Eser F, Kuşcu F, Tütüncü EE, Kul G, *et al*. Reactivation rates in patients using biological agents, with resolved HBV infection or isolated anti-HBc IgG positivity. Turk J Gastroenterol 2018;29:561-5.
18. Charpin C, Guis S, Colson P, Borentain P, Mattéi JP, Alcaraz P, *et al*. Safety of TNF-blocking agents in rheumatic patients with serology suggesting past hepatitis B state: Results from a cohort of 21 patients. Arthritis Res Ther 2009;11:R179.
19. Prestinari F, Ferguglia G, Laria G. Etanercept in a patient with severe psoriasis and latent viral hepatic disease and latent tuberculosis. Am J Clin Dermatol 2010;11 Suppl 1:57-8.
20. Nosotti L, Francesconi F, Izzi S, Berardesca E, Morrone A, Bonifati C. Safety of antitumour necrosis factor-α therapy in psoriatic patients with hepatitis B virus infection. Br J Dermatol 2010;162:1408-10.
21. Caporali R, Bobbio-Pallavicini F, Atzeni F, Sakellariou G, Caprioli M, Montecucco C, *et al*. Safety of tumor necrosis factor alpha blockers in hepatitis B virus occult carriers (hepatitis B surface antigen negative/anti-hepatitis B core antigen positive) with rheumatic diseases. Arthritis Care Res (Hoboken) 2010;62:749-54.
22. Fotiad`ou C, Lazaridou E, Ioannides D. Safety of anti-tumour necrosis factor-α agents in psoriasis patients who were chronic hepatitis B carriers: A retrospective report of seven patients and brief review of the literature. J Eur Acad Dermatol Venereol 2011;25:471-4.
23. Prignano F, Ricceri F, Pescitelli L, Zanieri F, Lotti T. Tumour necrosis factor-α antagonists in patients with concurrent psoriasis and hepatitis B or hepatitis C: A retrospective analysis of 17 patients. Br J Dermatol 2011;164:645-7.
24. Cassano N, Mastrandrea V, Principi M, Loconsole F, De Tullio N, Di Leo A, *et al*. Anti-tumor necrosis factor treatment in occult hepatitis B virus infection: A retrospective analysis of 62 patients with psoriatic disease. J Biol Regul Homeost Agents 2011;25:285-9.
25. Cho YT, Chen CH, Chiu HY, Tsai TF. Use of anti-tumor necrosis factor-α therapy in hepatitis B virus carriers with psoriasis or psoriatic arthritis: A case series in Taiwan. J Dermatol 2012;39:269-73.
26. Koskinas J, Tampaki M, Doumba PP, Rallis E. Hepatitis B virus reactivation during therapy with ustekinumab for psoriasis in a hepatitis B surface-antigen-negative anti-HBs-positive patient. Br J Dermatol 2013;168:679-80.
27. Laurenti R, Giovannangeli F, Gubinelli E, Viviano MT, Errico A, Leoni L, *et al*. Long-term safety of anti-TNF adalimumab in HBc antibody-positive psoriatic arthritis patients: A retrospective case series of 8 patients. Clin Dev Immunol 2013;2013:410521.
28. Navarro R, Vilarrasa E, Herranz P, Puig L, Bordas X, Carrascosa JM, *et al*. Safety and effectiveness of ustekinumab and antitumour necrosis factor therapy in patients with psoriasis and chronic viral hepatitis B or C: A retrospective, multicentre study in a clinical setting. Br J Dermatol 2013;168:609-16.
29. Notarnicola A, Iannone F, Lopalco G, Covelli M, Lapadula G. A false occult hepatitis B virus infection developed in a patient with psoriatic arthritis under infliximab and methotrexate therapy. Reumatismo 2014;65:298-301.
30. Navarro R, Concha-Garzón MJ, Castaño C, Casal C, Guiu A, Daudén E. Outcome of patients with serology suggestive of past hepatitis B virus infection during antitumor necrosis factor therapy for psoriasis. Int J Dermatol 2014;53:909-11.
31. Sanz-Bueno J, Vanaclocha F, García-Doval I, Torrado R, Carretero G, Daudén E, *et al*. Risk of reactivation of hepatitis B virus ınfection in psoriasis patients treated with biologics: A retrospective analysis of 20 cases from the BIOBADADERM database. Actas Dermosifiliogr 2015;106:477-82.
32. Chiu HY, Hui RC, Huang YH, Huang RY, Chen KL, Tsai YC, *et al*. Safety profile of secukinumab in treatment of patients with psoriasis and concurrent hepatitis b or c: A multicentric prospective cohort study. Acta Derm Venereol 2018;98:829-34.
33. Nard FD, Todoerti M, Grosso V, Monti S, Breda S, Rossi S, *et al*. Risk of hepatitis B virus reactivation in rheumatoid arthritis patients undergoing biologic treatment: Extending perspective from old to newer drugs. World J Hepatol 2015;7:344-61.

Original Article

The Effect of Coenzyme Q10 on Serum Glutathione Peroxidase Levels and Severity of Acne Vulgaris

Maria Leleury, Diah Adriani, Retno Indar Widayati, Kabulrachman, Asih Budiastuti, Muslimin

Department of Dermatovenereology, Faculty of Medicine, Diponegoro University, Semarang, Indonesia

Abstract

Objective: The objective of the study was to study the effect of coenzyme Q10 (CoQ10) supplementation on serum glutathione peroxidase (GSH-Px) levels and the severity of acne vulgaris (AV). **Methods:** A double-blind randomized controlled trial was carried out on 36 patients with AV classified according to severity. These patients were randomly divided into two groups (treatment group = 18 patients treated with tretinoin 0.025% cream and once-daily supplementation with a CoQ10 100 mg tablet; placebo group = 18 patients treated with tretinoin 0.025% cream and a once-daily placebo tablet). Blood samples were taken from a vein and examined by enzyme-linked immunosorbent assay. The study period was 8 weeks. Response to treatment was determined based on serum GSH-Px level and AV severity. The study used a pre- and post-test design for the two groups. The data were processed with SPSS for Windows version 25. **Results:** Administration of CoQ10 to AV significantly improved the severity of AV after 8 weeks compared to a placebo ($P = 0.008$). Serum GSH-Px levels after treatment with CoQ10 increase higher in the study than control group, but the statistical test result showed not significant in the study group ($P = 0.3$) and also control group ($P = 0.07$). **Conclusion:** CoQ10 supplementation may increase serum GSH-Px levels and improve the severity of AV, but there was no relationship between serum GSH-Px levels and the severity of AV.

Keywords: Acne vulgaris, coenzyme Q10, glutathione peroxidase, oxidative stress, tretinoin

Introduction

Acne vulgaris (AV) is a chronic inflammatory disease of the pilosebaceous follicular unit with multifactorial causes.[1] Recent research has shown an increase in total cases among a sample of 26–44-year-old females.[2,3] In Indonesia, in 2008, AV affected 15.3% of cases at the Dermatovenerology clinic of Dr. Kariadi General Hospital, Semarang, representing the tenth most prevalent skin condition.[4]

AV is characterized by inflammatory papules, pustules, and nodules, as well as noninflammatory open or closed comedones. Affected sites are chiefly on the face but can also include the upper arms, trunk, and back.[5] The Indonesian Acne Expert Meeting in 2012 recommended the use of the Lehmann grading system, which categorizes acne as mild, moderate, or severe.[6]

In terms of etiology, four crucial factors are thought to be involved in acne pathology: *Propionibacterium acnes*, responsible for the production of pro-inflammatory mediators by the immune system; sebaceous gland hypersecretion of sebum; hyperkeratosis leading to obstruction of the follicle; and inflammatory factors produced by the skin and immune system. Recent studies have suggested that various mechanisms and molecular pathways link oxidative stress to the pathogenesis of AV: toll-like receptors, peroxisome proliferator-activated receptors, the innate immune system, and mechanistic target of rapamycin.[4] An imbalance in the production of oxygen-derived prooxidants, also known as reactive oxygen species (ROS), and the cellular capacity of antioxidant defense is believed to lead to oxidative stress. Normally, ROS are removed by antioxidant enzymes in the cell, such as glutathione peroxidase (GSH-Px), catalase (CAT), and superoxide dismutase (SOD).[7]

Address for correspondence: Dr. Maria Leleury, Department of Dermatovenereology, Faculty of Medicine, Diponegoro University, Semarang, Indonesia.
E-mail: marialeleury@gmail.com

Submission: 15-05-2020 **Revision:** 05-07-2020
Acceptance: 16-07-2020 **Web Publication:** 17-09-2020

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/TJD.TJD_51_20

How to cite this article: Leleury M, Adriani D, Widayati RI, Kabulrachman, Budiastuti A, Muslimin. The effect of coenzyme Q10 on serum glutathione peroxidase levels and severity of acne vulgaris. Turk J Dermatol 2020;14:71-5.

GSH-Px is a group of important antioxidant enzymes. GSH-Px is the general name of an enzyme family with peroxidase activity, whose main biological role is protection from oxidative damage caused by ROS. The biological functions of GSH-Px are to reduce lipid hydroperoxide to its corresponding alcohol and reduce free hydrogen peroxide to water.[8,9]

Many therapeutic options are available for AV, including topical, systemic, and adjuvant therapies. The Global Alliance to Improve Outcomes in Acne published recommendations for the management of acne as a supplement to the *Journal of the American Academy of Dermatology* in 2003. The update also included a new way of considering acne as a chronic disease, a discussion of the changing role of antibiotics in acne management as a result of concerns about microbial resistance, and factors that affect adherence to acne treatments.[10] Oxidative stress may be implicated in the origin of acne, and antioxidant supplements may be valuable adjuvants in acne treatment.[11]

Coenzyme Q10 (CoQ10), also known as ubiquinone, is a lipid-soluble substance whose primary role is as an essential intermediate of the electron transport system in the mitochondria. Adequate amounts of CoQ10 are necessary for cellular respiration and ATP production. It significantly enhances antioxidant enzymes and regenerates tocopherol and ascorbic acid.[12] A typical CoQ10 dosage is 30–90 mg/day, but the recommended amount can be as high as 200 mg/day, and dosage >150 mg/day provides rapid and sustainable antioxidant and clinical improvement after 8 weeks of supplementation.[13,14]

CoQ10 treatment does not cause serious adverse effects in humans, and new formulations have been developed that increase CoQ10 absorption and tissue distribution. CoQ10 administered by oral and topical.[15] Topical CoQ10 application showed beneficial effects on mitochondrial membrane potential by reaching the vital layers of the skin, exerts antioxidant effects, and maintain the cellular energy levels.[16]

Oral administration of CoQ10 is a frequent antioxidant strategy in many diseases, which may provide a significant symptomatic benefit.[14,15] Therefore, this study investigated the effect of CoQ10 supplementation on serum GSH-Px levels and the severity of AV.

Methods

Research design

This study was performed between December 2019 and February 2020. Thirty-six women clinically diagnosed with AV, who attended the Outpatient Department of Dermatology and Venereology at Dr. Kariadi General Hospital, were enrolled in the study. Before initiation, each participant was informed about the aim of the study and signed an informed consent. Ethical approval for this study was obtained from Dr. Kariadi General Hospital Ethical Committee (380/EC/KEPK-RSDK/2019).

The inclusion criteria were mild-to-moderate-severe AV patients, female, aged 20–40 years, normal body mass index, mild-to-normal stress level (assessed by Beck's Depression Inventory), not taking drugs (antibiotics, anti-inflammatories, beta-blocker antihypertensives, statin antihyperlipidemics, warfarin, vitamins, or antioxidants) in the past 1 month, not pregnant and breastfeeding, not smoking, and willing to take part in the study to completion. The exclusion criteria were patients whose blood samples could not be collected due to technical factors and patients who refused blood sample collection.

The 36 patients were randomly allocated into two groups.

$$N1 = N2 = \left[\frac{(1.96 + 0.84) \times 3.3}{(26.9 - 23.6)}\right]^2$$

$$= 16$$

The minimum sample required was calculated as 16. Anticipating a nonresponse or dropout rate of 10%, a sample size of 18 for each group was set.

The first group of 18 patients was treated with tretinoin 0.025% cream and one CoQ10 100 mg oral tablet per day. The second group of 18 patients was treated with tretinoin 0.025% cream and one oral placebo tablet per day. The use of sunscreen cream with SPF 30 was suggested during the study period.

The diagnosis of AV was based on the total lesion count of comedones, papules, pustules, nodules, and cysts, according to the Lehmann criteria of AV severity. The duration required for each patient to complete the course of treatment was 8 weeks, with clinical and laboratory assessments carried out at baseline and the end of this period. Adverse effects were investigated by asking patients about any abnormal effect that appeared throughout the whole course of treatment.

Sample analysis

Blood samples for GSH-Px analysis were collected between December 2019 and February 2020. Samples of 3 mL were collected by venipuncture and allowed to clot for 2 h overnight at 2°C–8°C before centrifuging for 15 min at 1000 xg and 2°C–8°C. Serum GSH-Px was examined by enzyme-linked immunosorbent assay.

Statistical analysis

The data obtained were processed with SPSS software for Windows version 25 (IBM, New York, USA). Analysis used the paired *t*-test, Wilcoxon test, Mann–Whitney test, McNemar test, and Chi-square test to compare pre- and post-treatment values between the two groups. The significance level was set at $P \leq 0.05$. The Spearman correlation test was used to compare between serum GSH-Px level and severity of AV. The degree of relationship was expressed by the magnitude of the correlation coefficient. Intention to treat analysis was used in this study.

Results

Table 1 shows the demographic characteristics of each group. The mean age in the study group was 25.9 ± 4.52 years, and in the control group 26.5 ± 5.82 years. Statistical test results showed no significant difference in group ages (P = 0.9; Mann–Whitney test). The most common occupation in the study group was student (44.4%) and office worker in the control group (33.3%); statistical results were not significant (P = 0.1; Fisher's exact test). In the study group, 55.6% reported no sun exposure compared to 50% of the control group; the difference was not significant (P = 0.7; χ^2 test).

Figure 1 shows that, in study groups, serum GSH-Px levels higher than in the control group after treatment. Table 2 shows that serum GSH-Px levels increased from 518.3 ± 160.04 pg/mL to 1382.6 ± 740.55 pg/mL in the study group, which was not significant (P = 0.3; Mann–Whitney test). In the control group, levels increased from 549.3 ± 325.16 pg/mL to 1,036.2 ± 646.60 pg/mL, which was also not significant (P = 0.07; Mann–Whitney test). The result showed that the levels of serum GSH-Px in the study group was higher than in control group. But the statistical test results showed not significant.

The serum GSH-Px delta in the study group of 864.3 ± 631.95 pg/mL was significantly higher than the control group delta of 486.9 ± 549.81 pg/mL (P = 0.03; Mann–Whitney test).

Table 3 shows the severity of AV based on the Lehmann scoring criteria in the study and control groups. Statistical test results showed the change in the severity in the study group was significant (P = 0.008; McNemar test), whereas the change in the severity in the control group was not significant (P = 0.05; McNemar test).

Table 3 also shows the average serum GSH-Px level before treatment. The lowest level was in the severe group at 485.4 ± 237.62 pg/mL, whereas the highest level was in the moderate group at 603.4 ± 309.69 pg/mL. Statistical test results showed the differences in serum GSH-Px levels based on the

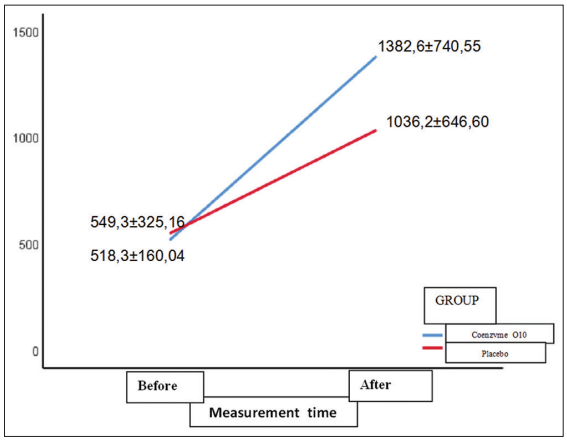


Figure 1: Shows that the control and study groups showed a increase in serum GSH-Px levels from before to after treatment. The Effect Of Coenzyme Q10 on Serum Gluthation Peroxidase Levels and Severity Of Acne Vulgaris

Table 1: Demographic characteristics of the study participants

Characteristic	Group		P
	Study (n=18)	Control (n=18)	
Age (years): mean±SD	25.9±4.52	26.5±5.82	0.9*
median (minimum-maximum)	25 (21-33)	25 (20-40)	
Occupation, n (%)			
Doctor	7 (38.9)	4 (22.2)	0.1§
Student	8 (44.4)	5 (27.8)	
Business	1 (5.6)	6 (33.3)	
Midwife	2 (11.1)	1 (5.6)	
Housewife	0 (0.0)	2 (11.1)	
Sun exposure, n (%)			
No	10 (55.6)	9 (50.0)	0.7¶
Yes	8 (44.4)	9 (50.0)	

*Mann–Whitney test, §Fisher's exact test, ¶ χ^2 test. SD: Standard deviation

Table 2: Effect of coenzyme Q10 on serum glutathione peroxidase levels

Measurement time	GSH-Px serum level (pg/mL) Mean±SD Median (minimum-maximum)		P¥
	Study group (n=18)	Control group (n=18)	
Before	518.3±160.04 502.0 (279.7-866.1)	549.3±325.16 405.6 (286.1-1,221.7)	0.3
After	1,382.6±740.55 1,251.1 (475.7-2,870.0)	1,036.2±646.60 778.2 (536.6-2,696.4)	0.07
Delta	864.3±631.95 754.4 (136.7-2,113.3)	486.9±549.81 300.6 (131.2-2,275.5)	0.03
P§ before versus after	<0.001	<0.001	

¥Mann–Whitney test, §Wilcoxon test. Delta: GSH-Px serum after – GSH-Px serum before, GSH-Px: Glutathione peroxidase, SD: Standard deviation

Table 3: Average serum glutathione peroxidase level before and after treatment by acne vulgaris severity based on Lehmann scoring criteria

Acne severity	GSH-Px serum level pg/mL Mean±SD; median (minimum-maximum)
Before treatment	
Mild (n=12)	512.6±207.54; 434.2 (318.0-1,009.6)
Moderate (n=12)	603.4±309.69; 499.7 (301.6-1,221.7)
Severe (n=12)	485.4±237.62; 440.6 (279.7-1,189.1)
After treatment	
Mild (n=24)	1,249.9±741.28; 944.4 (475.7-2,870.0)
Moderate (n=11)	1,152.3±684.06; 936.5 (576.9-?.4)
Severe (n=1)	866.1±0.00; 866.1 (866.1-866.1)

Kruskal–Wallis test: Before treatment P=0.7, After treatment P=0.9. GSH-Px: Glutathione peroxidase, SD: Standard deviation

severity of AV before treatment were not significant ($P = 0.7$; Kruskal–Wallis test). After treatment, the highest serum GSH-Px level was in the mild group at 1249.9 ± 741.28 pg/mL. The lowest was in the severe group at 866.1 ± 0.00 pg/mL. Statistical test results showed that the differences in serum GSH-Px levels based on the severity of AV after treatment were also not significant ($P = 0.3$; Kruskal–Wallis test).

Table 4 shows that the lowest GSH-Px delta decrease was 131.17 pg/mL in the control group with severe AV before treatment and moderate AV after treatment. The biggest increase was 2275.53 pg/mL in the control group with moderate AV before and after treatment. Statistical test results showed no correlation between serum GSH-Px level and AV severity ($P = 0.7$).

Table 4: Delta serum glutathione peroxidase and acne severity

Acne severity		Group	Delta serum GSH-Px (pg/mL)
Before	After		
Mild	Mild	Study	406.75
Mild	Mild	Study	423.37
Mild	Mild	Study	2,023.18
Mild	Mild	Study	1,687.71
Mild	Mild	Study	771.23
Mild	Mild	Study	149.69
Mild	Mild	Control	156.30
Mild	Mild	Control	806.32
Mild	Mild	Control	321.17
Mild	Mild	Control	240.32
Mild	Mild	Control	197.99
Mild	Mild	Study	310.45
Moderate	Mild	Study	303.42
Moderate	Moderate	Study	1,040.49
Moderate	Mild	Study	1,560.28
Moderate	Mild	Study	393.91
Moderate	Moderate	Study	156.13
Moderate	Mild	Study	2,113.27
Moderate	Mild	Control	134.3
Moderate	Mild	Control	205.22
Moderate	Mild	Control	1,478.2
Moderate	Moderate	Control	258.62
Moderate	Moderate	Control	328.1
Moderate	Moderate	Control	2,275.53
Severe	Mild	Study	567.31
Severe	Moderate	Study	1,132.96
Severe	Mild	Study	956.2
Severe	Moderate	Study	737.51
Severe	Mild	Study	998.09
Severe	Mild	Study	136.69
Severe	Moderate	Control	199.2
Severe	Moderate	Control	290.83
Severe	Mild	Control	480.83
Severe	Moderate	Control	557.98
Severe	Moderate	Control	131.17
Severe	Severe	Control	392.08

GSH-Px: Glutathione peroxidase

Discussion

This study measured serum GSH-Px levels before and after treatment in a study group with CoQ10 supplementation and a control group. In the study group, levels significantly increased ($P < 0.001$; Wilcoxon test). These results are similar to those of studies conducted by Hormozi in Iran in 2018. Supplementation with CoQ10 has an important role in preventing lipid peroxidation and protecting tissue against oxidative damage. In fact, by scavenging ROS, CoQ10 can be indirectly involved in regulating gene expression and modulating the activities of most enzymes. Thus, this antioxidant may alter the activity of many enzymes, especially oxidative damage repair enzymes.[17] In the control group, serum GSH-Px levels also significantly increased ($P < 0.001$; Wilcoxon Test). The skin synthesizes hydrogen peroxide to fight acne inflammation, and this can continue for several weeks until the inflammation resolves. The primary natural defense against free radicals is the prevention of their formation by various enzymes, especially GSH-Px, which regulates hydrogen peroxide levels by catalyzing the dismutation of H_2O_2 to $H_2O + CO_2$. Thus, the serum GSH-Px level increase in the control group may be due to the progress of inflammation in the pathogenesis of the disease.[18]

This study also assessed the severity of AV based on Lehmann criteria scoring. The change in severity in the study group was significant ($P = 0.008$; McNemar test). CoQ10, as an antioxidant, is essential for ATP synthesis. CoQ10 supplementation decreases lipid peroxidation by increasing antioxidant ability and removing free radicals.[19]

Statistical test results from this study showed that differences in serum GSH-Px levels based on the severity of AV before treatment were not significant ($P = 0.7$; Kruskal–Wallis test). The difference in levels based on the severity of AV after treatment was also not significant ($P = 0.3$; Kruskal–Wallis test). This result is similar to those of Aybey *et al*. in 2005, who found no significant difference in serum GSH-Px levels by the severity of AV.[20]

Conclusion

CoQ10 supplementation as an adjuvant therapy for AV can increase serum GSH-Px levels and improve the severity of AV, but there is no relationship between serum GSH-Px levels and the severity of AV.

Recommendation

Future studies are necessary for understanding the relationships between GSH-Px and other antioxidant enzymes such as SOD, CAT, and MDA as indicators of oxidative stress. Air pollution and pro-inflammatory factors may improve our ability to develop interventions to decrease oxidative stress.

Acknowledgment

Authors thank all the study participants contributing to this research.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Zaenglein AL, Graber EM, Thiboutot DM. Acne Vulgaris and Acnei form Eruptions. 8th ed. New York: Mc-Graw Hill; 2012.
2. Kardeh S, Moein SA, Namazi MR, Kardeh B. Evidence for the important role of oxidative stress in the pathogenesisof acne. Galen Medical Journal 2019;8:1291.
3. Collier CN, Harper JC, Cafardi JA, Cantrell W, Wang W, Foster KW, *et al*. The prevalence of acne in adults 20 years and older. J Am Acad Dermatol 2008;58:56-9.
4. Susanto SD. Epidemiologi Akne. Seminar and Workshop Acne Handling. Semarang 21-22 Maret; 2009.
5. Baumann L, Saghari S. Acne vulgaris. In: Baumann L, Saghari S, Weisberg E, editors. Cosmetic Dermatology. 2th ed. New York: McGraw-Hill; 2009.
6. Wasitaatmadja SM. Akne, Erupsi akneiformis, rosasea, rinofima. In: Djuand A, Hamzah M, Aisah S, editors. Ilmu Penyakit Kulit dan Kelamin. 6th ed. Jakarta: Medical Faculty of Indonesia University; 2010.
7. Baumann L, Saghari S. Antioksidan. Dalam: Baumann L, Saghari S, Weisberg E, editors. Cosmetic Dermatology. 2th ed. New York: McGraw-Hill; 2009.
8. Gerontol MU. Glutathione peroxidase enzyme system. J Am Acad Dermatol 2007;25:405.
9. Thiboutot D, Gollnick H, Bettoli V, Dreno B, Kang S, Leyden J, *et al*. New insights into the management of acne : An update from the global alliance to improve outcomes in acne group. J Am Acad Dermatol 2009;60:S1-50.
10. Agniseszka S, Alicja K. Significance of diet and oral supplementation in acne vulgaris. EMJ Dermatol 2016;4;90-4.
11. Juan M. Coenzyme Q_{10} therapy. Mol Syndromol 2014;5:187-97.
12. Lee B. Effects of coenzyme Q10 supplementation (300 mg/day) on antioxidation and anti-inflammation in coronary artery disease patients during statins therapy: A randomized, placebo-controlled trial. Nutr J 2013;12:142.
13. Saini R.Coenzym Q10: The essential nutrient. J Pharm Bioallied Sci 2011;3:466-7.
14. Bank G, Kagan D, Madhavi D. Coenzyme Q10: Clinical update and bioavailability. J Evid Based Complement Altern Med 2011;16:129-37.
15. Hormozi M, Mirzaei R, Nakhaee A, Payandeh A, Izadi S, Haghighi JD. Effects of coenzyme Q10 supplementation on oxidative stress and antioxidant enzyme activity in glazers with occupational cadmium exposure: a randomized, double-blind, placebo-controlled crossover clinical trial. Med Toxicol 2019;35:32-42.
16. Knott A, Achterberg V, Smuda C, Mielke H, Sperling G, Dunckelmann K, *et al*. Topical treatment with coenzyme Q10-containing formulas improves skins Q10 level and provides antioxidant effects. Biofactors 2015;41:383-90.
17. Al-Hamadani K, Ewadh M, Shemran KA. The relation with glutathione peroxidase, trace elements in patients with acne vulgaris. Int J Appl Biol Pharm Technol 2011;2:74-80.
18. Rotig A. News in ubiquinone biosynthesis. Chem Biol 2010;17:415-16.
19. Aybey B. Glutathione peroxidase enzyme levels of patient with acne vulgaris. J Eur Acad Dermatol Venereol 2005;19:766-7.
20. Basak PY, Gusltekin F, Kilinc I. The role of antioxidant defence system in papulopustular acne. J Dermatol 2001;28:123-7.

Case Report

Psoriasis Presenting as Targetoid Lesions: First of Its Kind

Pallavi Goyal[1,2], Surabhi Dayal[2], Priyadarshini Sahu[2]

[1]Department of Dermatology, Kalpana Chawla Government Medical College, Karnal, [2]Department of Dermatology, Venereology and Leprosy, Pt. B. D. Sharma PGIMS, Rohtak, Haryana, India

Abstract

Psoriasis is a common chronic inflammatory and proliferative condition of the skin and its presentation as targetoid lesions has not been described. A 29-year-old male came to the outpatient department with multiple red color elevated skin lesions over the forehead and trunk for the past 10 days. Multiple targetoid lesions of size 2 cm × 2 cm to 5 cm × 4 cm having central edematous crusted zone and the peripheral zone of erythema with irregular to well-defined margins present almost all over the body. Differential diagnosis included psoriasis, erythema multiforme, pemphigus erythematosus, and reiter's disease. The biopsy confirmed the diagnosis of psoriasis. The patient was started on injection methotrexate and responded well.

Keywords: Methotrexate, psoriasis, targetoid lesions

Introduction

Targetoid lesions also called as atypical targets have been described with disorders such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), ecthyma gangrenosum, fixed drug eruption, vasculitis, erythema chronicum migrans, granuloma annulare, connective tissue diseases, and certain autoimmune blistering diseases.[1] There are diverse forms of psoriasis-like chronic plaque, pustular, guttate, sebopsoriasis, napkin, inverse, erythrodermic and atypical forms such as rupioid, elephantine, Blaschko linear, and segmental. We are hereby reporting a case where psoriasis clinically presented as targetoid lesions, which has not been described as yet.

Case Report

A 29-year-male, an electrician by occupation presented with multiple red colored elevated skin lesions over the forehead and trunk for 10 days. Initially, he started developing lesions over the chest associated with mild itching, which gradually increased in size and progressed to involve the forehead, back, and extremities. Later patient took multiple doses of steroid injections (dexamethasone) from some village practitioner, which led to an exacerbation of the lesions. There was no history of any other drug intake, fever, photosensitivity, oral ulcers, Raynaud's phenomenon, urticaria, joint pain, and extramarital sexual contact. The patient denied of having any blistering disorders in the past. The patient did not have any previous episodes of similar illness in the past. Family history was not found to be significant. Both oral and genital mucosa, palms and soles, scalp, and nails were normal.

On cutaneous examination, there were multiple targetoid lesions of size 2 cm × 2 cm to 5 cm × 4 cm having central edematous crusted zone and the peripheral zone of erythema with irregular to well-defined margins, present almost all over the body [Figure 1]. A punch biopsy was done from a skin lesion over the chest. Psoriasis, EM, pemphigus erythematosus, and reiter's disease were kept as the differential diagnoses. Histopathology features revealed hyperkeratosis, parakeratosis, neutrophilic collections, the formation of spongiotic pustules in the upper portion along with marked elongation of the rete ridges and upper dermis showed moderately intense perivascular inflammatory

Submission: 29-04-2020 **Revision:** 30-05-2020
Acceptance: 09-06-2020 **Web Publication:** 17-09-2020

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/TJD.TJD_41_20

Address for correspondence: Dr. Pallavi Goyal, Pawan Surgical Hospital, Red Road, Kurukshetra - 136 118, Haryana, India.
E-mail: drpallavigoel@gmail.com

How to cite this article: Goyal P, Dayal S, Sahu P. Psoriasis presenting as targetoid lesions: First of its kind. Turk J Dermatol 2020;14:76-8.

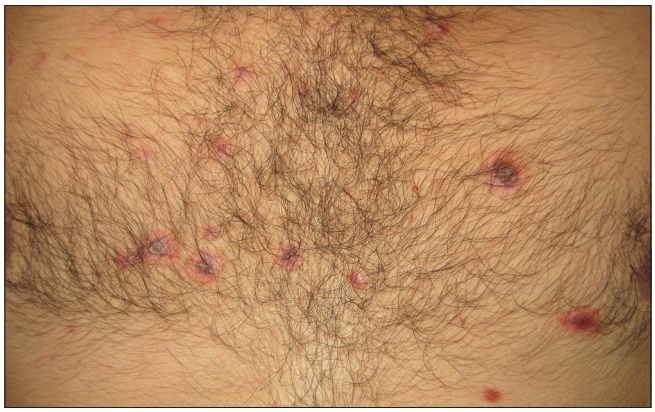


Figure 1: Multiple targetoid lesions of size 2 cm × 2 cm to 5 cm × 4 cm having central edematous crusted zone and the peripheral zone of erythema present over the chest

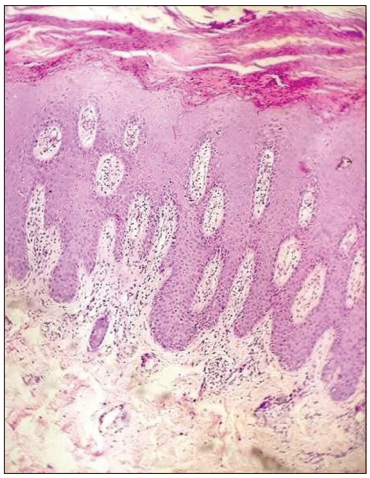


Figure 2: Photomicrographs showing hyperkeratosis, parakeratosis, loss of granular layer, acanthosis, neutrophilic collections with marked elongation of rete ridges. The upper dermis shows perivascular inflammatory infiltrate (H and E, ×10)

infiltrate; which were suggestive of psoriasis [Figure 2]. Classical changes of psoriasis include parakeratosis with focal orthokeratosis and accumulation of neutrophils in the stratum corneum, spongiform pustules in the Malphigian layer, elongation of rete ridges and suprapapillary epidermal thinning. Dilated, tortuous papillary blood vessels are surrounded by mixed mononuclear and neutrophil infiltrate as well as extravasated erythrocytes.[2]

Routine investigations such as complete blood count, liver function test, renal function test, lipid profile, fasting and postprandial blood sugar, urine examination (routine and microscopic), human immunodeficiency virus enzyme-linked immunosorbent assay test, hepatitis B antigen, anti-hepatitis C virus antibodies, thyroid function test, venereal disease research laboratory test, chest X-ray, electrocardiography were performed to rule out any systemic involvement and to plan further treatment. Antinuclear antibodies titer was found to be negative. The patient was found to be diabetic. All other investigations were normal. The patient was started on injection methotrexate 7.5 mg given intravenously once weekly. The patient was regular with follow-up and responded well.

Discussion

Targetoid lesions (also called as atypical targets) consist of two zones- central zone of erythema in the form of a papule, macule, or vesiculation; surrounded by a peripheral zone of erythema. Till today, targetoid lesions have been associated with EM, SJS, TEN, ecthyma gangrenosum, fixed-drug eruption, EM-like reactions, vasculitis, acute hemorrhagic edema of infancy, erythema chronicum migrans, granuloma annulare, pruritic urticarial papules and plaques of pregnancy, targetoid hemangioma, targetoid nevus, connective tissue diseases, and certain autoimmune blistering diseases.[1,3]

Psoriasis belongs to a group of chronic inflammatory and proliferative conditions of the skin. Most typical lesions consist of red, sharply demarcated, indurated plaques with silvery-white scales present particularly over extensor surfaces and the scalp. Morphological variants are common. There are various types of psoriasis-like chronic plaque, pustular, guttate, sebopsoriais, napkin, inverse, erythrodermic which had been described in the literature. Other atypical forms are rupioid, elephantine, Blaschko linear, and segmental psoriasis. Plaque psoriasis is the most common type of psoriasis, accounting for about 80%–90% of all cases.[2] However, the targetoid type of psoriasis had not been reported till now. Although, targetoid lesions which are a part of psoriasis secondary to administration of hydroxychloroquine had been described previously.[4] However, to the best of our knowledge, targetoid psoriasis which is idiopathic in nature has not been described previously. These targetoid lesions may be due to increased lymphocytic infiltrate at dermoepidermal junction, which could have led to such lesions in psoriasis. However, additional reports are needed to better characterize this type of psoriasis and to re-emphasize our observation. To conclude, treating dermatologists should have a high index of suspicion for psoriasis when a patient presents with targetoid lesions to avoid missing an important diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Madke B, Chougule B, Kar S, Khopkar U. Appearances in clinical dermatology. Indian J Dermatol Venereol Leprol 2014;80:432.
2. Burden DA and Kirby B. Psoriasis and related disorders. In: Griffiths CE, Barker J, Bleiker T, Chalmers RC, editors. Rook's Textbook of Dermatology. 9th ed. UK: Wiley Blackwell Publications; 2016. p. 35.1-35.30.
3. Hughey LC. Approach to the hospitalized patient with targetoid lesions. Dermatol Ther 2011;24:196-206.
4. Mccoy SS, Nagaraja V, Paviol S, Gudjonsson JE, Kahlenberg JM. Exacerbation of psoriasis due to hydroxychloroquine. Arch Med 2015;7:7-9.

A Case of Generalized Granuloma Annulare with Diabetes Mellitus: Regressed with Antidiabetic Therapy

Sir,

Granuloma annulare (GA) is a benign necrobiotic granulomatous dermatosis of unknown cause, presenting as localized, generalized, perforating or subcutaneous lesions.[1,2]

Diabetes has been reported to occur in up to 20% cases of GA.[3] We present a case with diabetes mellitus (DM) that was diagnosed while the patient was being investigated for generalized GA (GGA), and his lesions improved after institution of treatment for DM.

A 65-year-old male presented with multiple itchy skin-colored raised lesions on the trunk and extremities of 1-month duration. There was no prior history of drug intake or insect bite hypersensitivity.

Cutaneous examination revealed multiple, well-defined, skin-colored to slightly erythematous papules and nodules on the extremity [Figure 1a], back [Figure 1b], and abdomen. Few of the lesions showed central umbilication and crusting. General and systemic examinations were within normal limit.

We considered differential diagnoses such as perforating dermatoses, prurigo nodularis, and GA. The patient was asked to get investigations, especially blood glucose, done.

The fasting blood sugar was 250.15 mg/dl and postprandial blood sugar was 409.19 mg/dl. Biopsy showed palisading granuloma with central collagen degeneration [Figure 1c]. An Alcian blue stain showed mucin at the center of granuloma [Figure 1d]. Hence, we diagnosed the case as a GA.

The patient was given oral metformin 500 mg twice daily with glimepiride 2 mg once daily and antihistaminic.

After 3 weeks of his follow-up, we noticed that his blood sugar level became apparently normal and surprisingly, almost all GGA lesions also subsided, leaving behind postinflammatory hyper-pigmentation [Figure 1e and f]. There was no recurrence at 9 months of follow-up.

GA was described by Calcott Fox in 1895 and named by Radcliffe Crocker in 1902. It is a benign, inflammatory disorder of unknown etiology.[2]

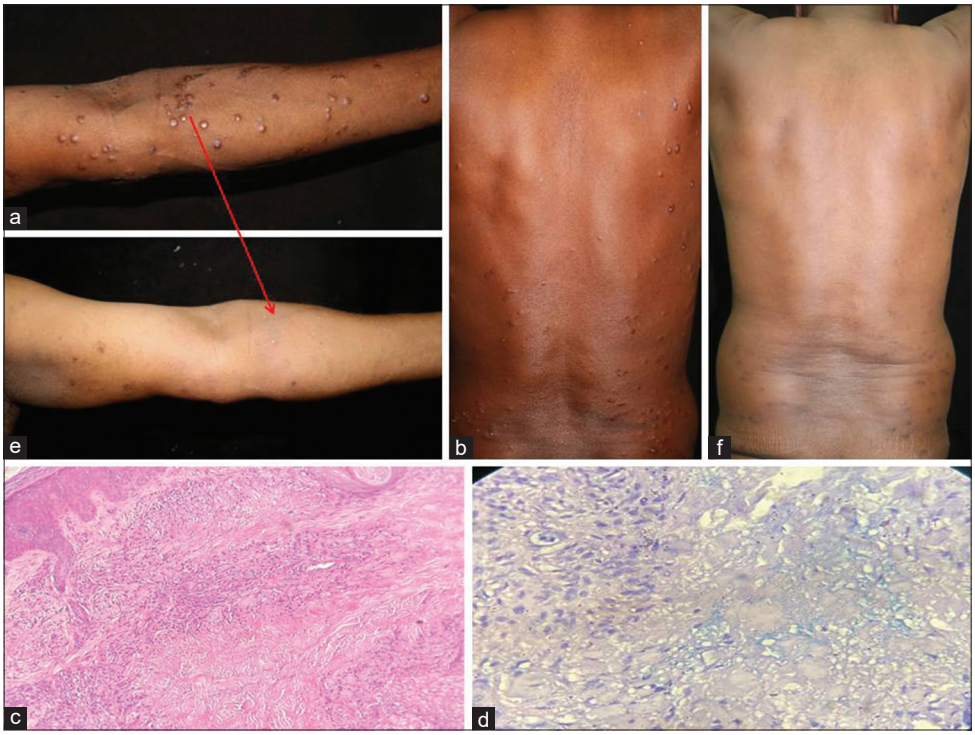


Figure 1: (a) Multiple, skin-colored, shiny papules with smooth surface on the inner aspect of the left upper extremity. (b) Multiple, skin-colored to hyperpigmented papules with central umbilication and crusting on the back. (c) Palisading granuloma in the superficial and mid dermis around the focus of mucin deposition and necrobiosis (H and E, ×10). (d) Mucin within the center of palisaded granuloma (Alcian blue, ×40). (e and f) After 3 weeks of antidiabetic therapy, the papular lesions completely resolved with residual hyper-pigmentation

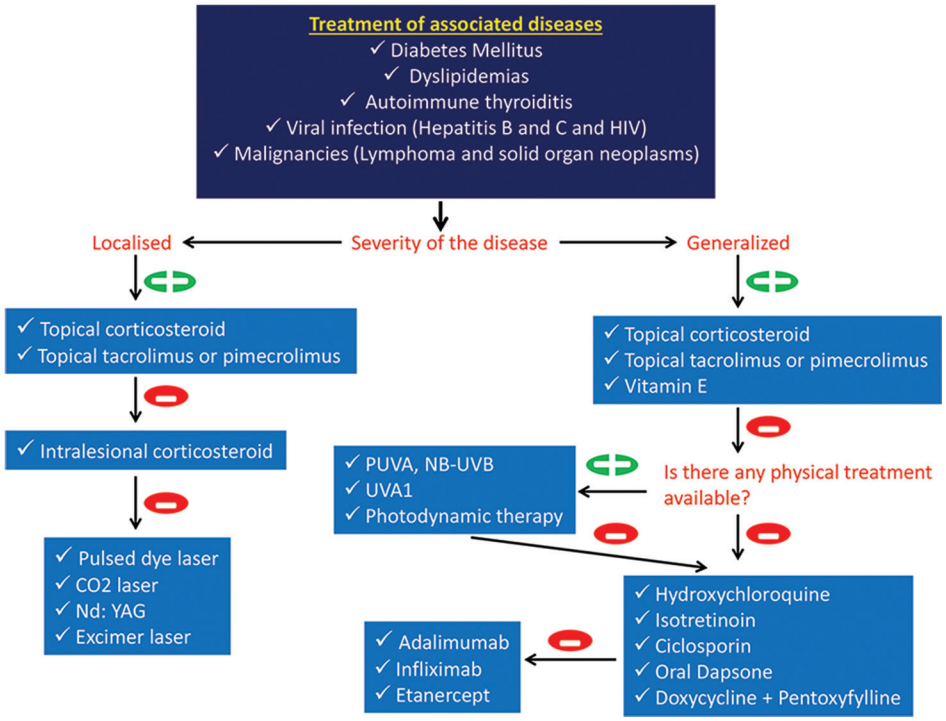


Figure 2: Treatment algorithm figure

How DM triggers GA is unknown. The increased serum glucose level or the resistance of insulin may change the structure of dermal blood vessels. Another possibility is that it can trigger the disease onset by damaging the structure of dermal collagen.

GGA in diabetes presents as a diffuse papular eruption, with pruritus being the prominent complaint. It differs from the localized form by a later age of onset, protracted course with only rare spontaneous resolution, poor response to therapy, and increased prevalence of human leukocyte antigen Bw 35.[4]

Most cases of GA resolve spontaneously. Though natural resolution is a possible mechanism, biopsy as a triggering factor for resolution cannot be ruled out. Muzeyyen *et al.*[5] noted that GGA lesions regressed after the regulation of serum glucose level with antidiabetic therapy and contributed to the information of relationship between GA and DM in the etiopathogenesis of GA.

Various methods are used in the treatment of GA [the treatment algorithm figure is depicted in Figure 2].

Although we cannot exclude the possibility of spontaneous regression of the lesions of GA in our patient, and the effect of biopsy-induced trauma on the disease course, we believe that the lesions regressed by instituting antidiabetic therapy, as the lesions were persisting and deteriorating for 1 month prior to the patient presenting to us.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Hari Pathave, Vaibhav Barve, Hanamant Gadade, Chitra Nayak

Department of Dermatology, BYL Nair Charitable Hospital and TNMC, Mumbai, Maharashtra, India

Address for correspondence: Dr. Hanamant Gadade, Department of Dermatology, BYL Nair Charitable Hospital and TNMC, Mumbai, Maharashtra, India.
E-mail: hanamantgadade03@gmail.com

References

1. Cohen PR, Carlos CA. Granuloma annulare mimicking sarcoidosis: Report of patient with localized granuloma annulare whose skin lesions show 3 clinical morphologies and 2 histology patterns. Am J Dermatopathol 2015;37:547-50.
2. Burns DA. Necrobiotic disorders. In: Burns T, Breathnach S, Cox NH, Griffiths C, editors. Rook's Text Book of Dermatology. 8th ed. Oxford: Wiley-Blackwell; 2010. p. 60.1-12.
3. Garg S, Baveja S. Generalized granuloma annulare treated with monthly rifampicin, ofloxacin, and minocycline combination therapy. Indian J Dermatol 2013;58:197-9.
4. Friedman-Birnbaum R, Haim S, Gideone O, Barzilai A. Histocompatibility antigens in granuloma annulare. Comparative study of the generalized and localized types. Br J Dermatol 1978;98:425-8.
5. Muzeyyen G, Secil S, Oguzhan K, Ulker G, Murat D. A case of

generalized granuloma annulare that contributed to the diagnosis of diabetes mellitus and regressed with antidiabetic therapy. Turkiye Klinikleri J Dermatol 2009;19:23-6.

Submission: 02-05-2020 **Revision:** 05-05-2020
Acceptance: 09-06-2020 **Web Publication:** 17-09-2020

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/TJD.TJD_43_20

How to cite this article: Pathave H, Barve V, Gadade H, Nayak C. A case of generalized granuloma annulare with diabetes mellitus: Regressed with antidiabetic therapy. Turk J Dermatol 2020;14:79-81.

Pinch Purpura: A Clinical Clue for Primary Systemic Amyloidosis

Sir,

Primary systemic amyloidosis is a group of monoclonal plasma cell disorders, characterized by extracellular deposition of immunoglobulin light chain fibrils in multiple organs leading to progressive multi-organ dysfunction. It is a rare disease which usually occurs in elderly persons and has a poor prognosis.[1] We report a 73-year-old female with peri-orbital purpura as presenting feature of primary systemic amyloidosis.

A 73-year-old diabetic female presented with complaints of generalized weakness, arthralgia, and peri-orbital purpura of 3-month duration. The purpuric lesions developed spontaneously and were not associated with any recent trauma. There was no prior history of intake of drugs. On examination, there were extensive purpuric lesions on the neck, inframammary areas, anterior abdominal wall, inguinal area, and cubital fossa in addition to peri-orbital areas [Figure 1a]. No other cutaneous lesions were seen elsewhere over the body. Oral mucosa was congested with ruptured hemorrhagic bullae. The tongue was enlarged; fissured and hemorrhagic bullae were present on the surface with restricted movements. Teeth indentation marks were found around its lateral border [Figure 1b]. Systemic examination was normal. Her hemogram was normal except her hemoglobin was 8 g/dl. No abnormal cells were found in the peripheral smear. Bleeding time, clotting time, prothrombin time, activated partial thromboplastin time, and International normalized ratio (INR) were normal. Bone marrow aspiration from the iliac crest revealed increased number of plasma cells (average: 13%). All relevant biochemical and serological tests were normal. Urine 24 h protein was 132 mg/day. Urinary Bence Jones proteins were absent. High-resolution serum protein electrophoresis revealed the presence of monoclonal gammopathy M spike in the gamma globulin region. Serum immunofixation electrophoresis revealed the presence of monoclonal gammopathy (M spike) as IgG and Lambda. Skin biopsy from the purpuric lesions showed eosinophilic amorphous homogenous deposits in the dermis and surrounding thin blood vessels in the reticular dermis; extensive extravasated Red blood cells (RBCs) were present [Figure 2]. Congo red staining showed characteristic apple green birefringence on polarized microscopy. Abdominal fat pad aspiration showed apple green birefringence on polarized microscopy [Figure 3]. Chest radiograph, skeletal survey of the body, ultrasound, and Computed tomography (CT) of the abdomen were normal. Electrocardiogram (ECG) and 2D Echocardiography (2D-ECHO) showed no significant abnormalities.

Based on the clinical features, histopathology, and biochemical findings, a diagnosis of primary systemic amyloidosis of Amyloid light-chain (AL) type was made.

Skin manifestations are seen in almost all three groups of primary systemic amyloidosis, and its involvement is 30%–40% of cases. Cutaneous manifestations comprise of petechiae or hemorrhages, peri-orbital purpura, waxy papules, nodules, plaques, bullous lesions, mucocutaneous infiltrates, macroglossia, and nail dystrophy.[1] Purpura, petechiae, and ecchymoses are the common, and these are caused with or without trauma. This purpura is called as pinch purpura.[2] The purpura typically occurs above the nipple line and is often seen in the webbing of the neck, peri-orbital areas, and the eyelids. Amyloid deposition in the skin and blood vessel wall causes capillary fragility and eventually causing intracutaneous micro- and macrohemorrhages.[3] Factor X deficiency resulting from the binding of factor X to amyloid fibrils, is thought to be another cause of bleeding diathesis.[4]

In this patient, the key presenting feature was peri-orbital purpura and scattered nontraumatic ecchymoses, without systemic involvement with normal hematological findings. This feature (pinch purpura) led us to consider the diagnosis of primary systemic amyloidosis (AL type). In majority of the

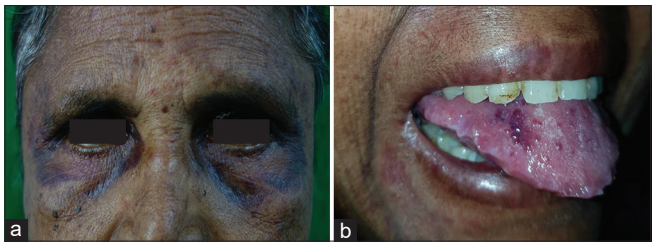


Figure 1: (a) Peri-orbital purpura (b) Hemorrhagic blisters and teeth indentation marks over the tongue

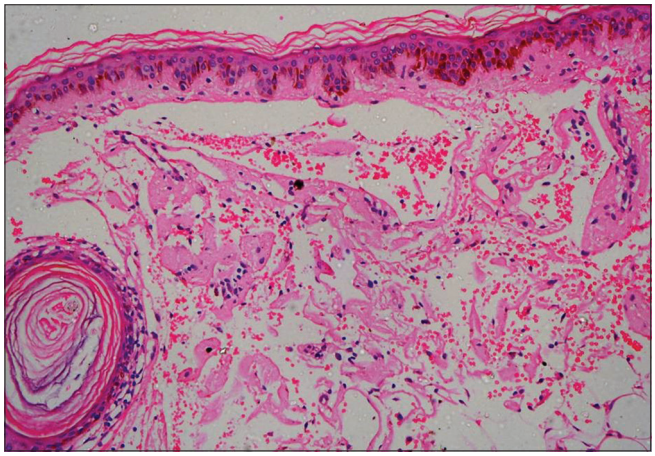


Figure 2: (H and E × 400) Normal epidermis with thin-walled blood vessels, seen with surrounding eosinophilic amorphous homogenous deposits. The deposits are also present in the dermis. The reticular dermis shows extensive extravasated RBCs. There is focal homogenization of the reticular dermis

published cases[5-7] also, pinch purpura is the early presenting manifestation. Recently, Zoe *et al*. reported an interesting case of pinch purpura with systemic amyloidosis, multiple myeloma, and subclinical cardiomyopathy.[8] Another case of peri-orbital inframammary purpura with left ventricular hypertrophy without any clinical history of hypertension was also reported.[3] The heart is the second most commonly affected organ next to renal involvement, which accounts for 75% of deaths in AL amyloid patients. Therefore, pinch purpura can be considered as an early cutaneous marker of this systemic disease.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Ashwini R. Mahesh, T. Satyaprakash[1], Deepak Joshi, Gandikota Raghurama Rao, Kollipara Haritha[2], A. Prasad Chowdary

Department of DVL, GSL Medical College, [1]Department of Pathology, GSL Medical College, Rajahmundry, [2]Department of DVL, GITAM Medical College, Visakhapatnam, Andhra Pradesh, India

Address for correspondence: Dr. Gandikota Raghurama Rao, Department of DVL, GSL Medical College, Rajanagaram, Rajahmundry - 533 296, Andhra Pradesh, India.
E-mail: graghuramarao@gmail.com

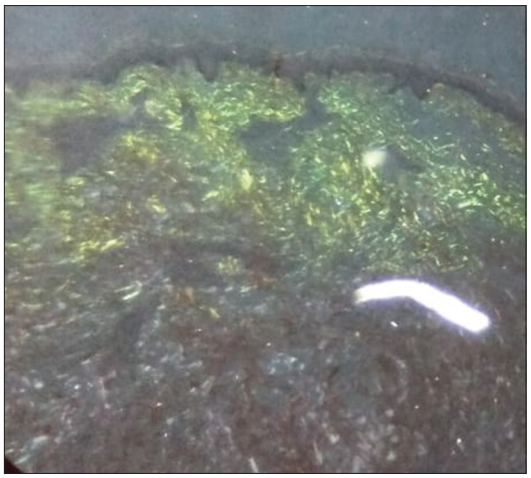


Figure 3: (×100) Congo red shows apple green birefringence under polarized light

References

1. Yamamoto T. Amyloidosis in the Skin, Amyloidosis-An Insight to Disease of Systems and Novel Therapies. Güvenç IA: In Tech; Rijeka, Croatia; 2011. p. 91-104.
2. Agarwal A, Chang DS, Selim MA, Penrose CT, Chudgar SM, Cardones AR. Pinch purpura: A cutaneous manifestation of systemic amyloidosis. Am J Med 2015;128:3-4.
3. Kelsey A, Smith DH, Meng J, Murphy M, Rothe MJ. Amyloidosis: A story of how inframammary erosions eclipsed inconspicuous periorbital ecchymoses. Int J Womens Dermatol 2016;2:18-22.
4. Lihieder HB. Amyloid purpura. N Engl J Med 2007;356:23.
5. Öztürk E, Akay MO, Ferhanoğlu B. Recognizing pinch purpura as the first manifestation of light-chain amyloidosis. Turk J Haematol 2018;35:208-9.
6. Saoji V, Chaudhari S, Gohokar D. Primary systemic amyloidosis: Three different presentations. Indian J Dermatol Venereol Leprol 2009;75:394-7.
7. Patil S, Chinthala S, Lunge S. Primary idiopathic systemic amyloidosis-Rare classical cases with fatal outcome. Our Dermatol Online 2016;7:294-8.
8. Apalla Z, Kirtsios TN, Katodritou E, Lallas A, Konstantinou D, Karamitsos T. Pinch purpura unmasking systemic amyloidosis. Int J Dermatol 2019;58:e195-6.

Submission: 31-05-2020 **Revision:** 06-07-2020
Acceptance: 16-07-2020 **Web Publication:** 17-09-2020

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/TJD.TJD_62_20

How to cite this article: Mahesh AR, Satyaprakash T, Joshi D, Rao GR, Haritha K, Chowdary AP. Pinch purpura: A clinical clue for primary systemic amyloidosis. Turk J Dermatol 2020;14:81-2.