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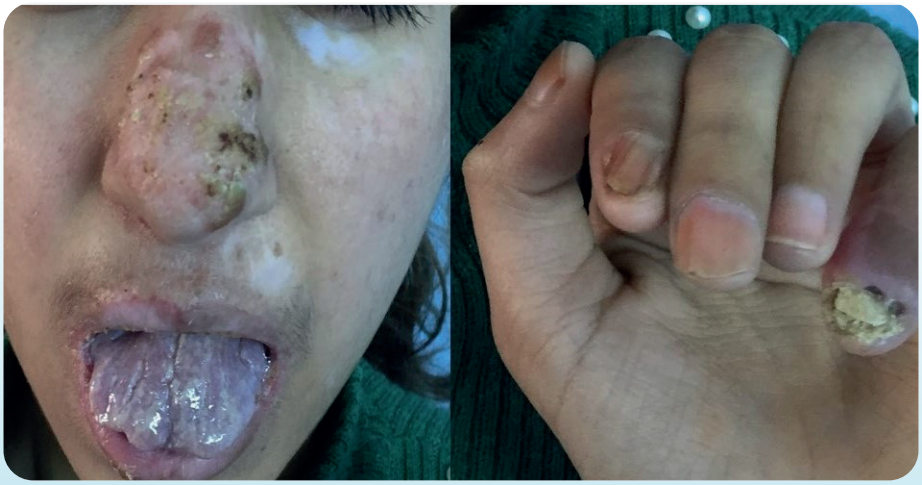

The effect of different mucosal thickness on implant crestal bone loss

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Murat Cakir

Dear colleagues,

After a short interruption, we are delighted to welcome you to the first issue of Mucosa in 2022. We have some changes in this new period. As of this year, Mucosa will be published three issues a year, in January, May and September. We also made some changes in our editorial board, we have new precious members and additional section editors in Pulmonary Medicine, Ophthalmology, Urology and Gynecology. We cordially thank the editorial board members who left us in this new period, and would like to welcome our new members warmly. Mucosa will continue to be a high scientific forum to discuss all aspects of mucosal tissues in different basic and clinical disciplines.

In this issue, we have five scientific articles for you. Yilmaz and Tunali reviewed the effects of mucosal thickness on the marginal bone loss in the implant area from the perspective of periodontology. In the research article section, Uzlu et al investigated the effects of systemic isotretinoin on retinal nerve fiber layer thickness (RNFL) and corneal cell density (CCD). They found decreased RNFL and central corneal thickness by optical coherence tomography.

Kavak et al reported a case series including six female patients with isolated vulvar purpura. They discussed if non-blanching purpura could be a component of plasma cell vulvitis or “mucosal porosis”.

Cowan et al reported a case of bullous pemphigoid (BP) triggered by the Oxford-AstraZeneca Vaxzevria COVID-19 vaccination and it is still one of the first cases of this COVID-19 vaccine-induced BP. Finally, Erat et al reported a rare case of chronic mucocutaneous candidiasis and drew attention to the coexisting endocrinopathies such as vitiligo.

We want to thank our readers, authors, reviewers, and our publisher for their meritorious contributions. We await your valuable contributions to our forthcoming issues in this new period of Mucosa.

Warm regards,

Murat Cakir
Savas Yayli

Editors-in-Chief

Review

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The effect of different mucosal thickness on implant crestal bone loss

Farklı mukozal kalınlıkların implant çevresi krestal kemik kaybına etkisi

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Abstract

A dental implant is a treatment option that is widely used nowadays and provides to giving the aesthetic, function, and phonation back to the patient in dental deficiencies. Nevertheless, the inefficacies of dental implants also draw attention for various reasons. Factors causing early period implant inefficacies are being analyzed and reasons that may be affecting marginal bone loss are being elaborated. In the literature, factors causing marginal bone loss such as premature prosthetic loading, neglected cement residues at the prosthesis stage, micro-gap foundation, infection foundation on the surgery region and traumatic surgery draws attention. One of these reasons is the thickness of the mucosa covering the region that the implant is placed (phenotype). The purpose of our review is to discuss the effect of mucosal thickness in the surgical area on the marginal bone loss in the implant area, within the scope of the literature.

Key words: *soft tissue thickness, marginal bone loss, crestal bone loss, dental implants*

Öz

Dental implantlar günümüzde sıklıkla kullanılan ve diş eksikliklerinde hastaların estetik, fonksiyon ve fonasyonunun iadesini sağlayan tedavi seçenekleridir. Buna rağmen, çeşitli nedenlere bağlı olarak, dental implantların başarısızlıkları da dikkati çekmektedir. Erken dönem implant başarısızlıklarına sebep olan faktörler araştırılmakta ve marjinal kemik kaybına etkisi olabilecek olan nedenlerin üzerinde durulmaktadır. Literatürde implant çevresi marjinal kemik kaybıyla ilgili araştırılan faktörler arasında prematür protetik yükleme, protez aşamasında göz ardı edilen siman artıkları, mikro aralık oluşumu, cerrahi sahada enfeksiyon oluşumu ve travmatik cerrahi gibi sebepler göze çarpmaktadır. Bu nedenlerden biri de implant yerleştirilecek sahayı örten mukozanın kalınlığıdır (fenotipi). Derlememizin amacı cerrahi yapılacak bölgedeki mukozal kalınlığın implant çevresi marjinal kemik kaybı üzerine etkisini güncel literatür desteğinde tartışmaktır.

Anahtar kelimeler: *yumuşak doku kalınlığı, marjinal kemik kaybı, krestal kemik kaybı, diş implantları*

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Introduction

Dental implants are widely used nowadays, and they are known as the gold standard treatments for dental deficiencies. Despite this extensive application area, it is important for dental implants to maintain their functional and aesthetic achievement in the long run. Risk factors causing implant failures are topics that are still being researched.[1]

Maintenance of the alveolar bone health, and especially the prevention of bone loss on the implant's neck area is the primary problem and research subject in the achievement of dental implants. In 1994, Alberktsson and Isidor[2] claimed that after 1 year from a successful dental implant loading, bone loss up to 1.5 mm on the marginal bone is clinically acceptable. Nowadays, this 1.5 mm bone loss is not acceptable for reasons of factors such as patient's growing aesthetic expectations, increasing average life, and it is tried to be prevented.[3] Various studies have been held to prevent marginal bone loss, such as the influence of the micro-gap between the implant-abutment, using platform-switch implant-abutment, the dental implant being positioned differently according to the alveolar crestal, modified surface usage on the neck area of the implant, impacts of different implant designs, decreasing the surgical trauma, effects of abnormal prosthetic loading. As a new viewpoint, soft tissue structure on the region where the implant will be placed and its quality's effect on the marginal bone loss have been started to be evaluated in scientific researches.

The purpose of our study is to make an updated literature review of the studies about the effect of mucosal thickness in individuals who have different mucosal thicknesses on the crestal bone loss.

Periodontal and peri-implanter mucosa

The soft tissue around the dental implant is named peri-implanter mucosa. The post-implant-surgery wound healing process determines the characteristics of peri-implanter mucosa. Soft tissue attachment occurs when the mucosa heals. This is called transmucosal attachment. Transmucosal attachment protects the bone from inside the oral cavity during osseointegration and rigid fixation.[4]

Supracrestal soft tissue attachment (biologic width)

The width of the tooth-facing of soft tissue is defined as biologic width of soft tissue. Gargulio et al. defined the connective tissue attachment, gingival crevicular and connection epithelium in a study they have done in 1961. As a result of the histometric measurements, they have determined that the connection epithelium right under the 1.07 mm connective tissue attachment and gingival crevicular is 0.97 mm on average. It is said that the total of 2.04 mm of these two values is the mean value of biologic width. Today, this area is called supacrestal soft tissue attachment.[5] Supracrestal soft tissue attachment occurs around implants like natural teeth. In the peri-implant region, it consists of a marginal epithelium surrounding the implant surface, called the epithelial attachment, and a connective tissue attachment consisting of collagen fibers adhering to the implant surface.[6] To avoid bacterial penetration and protect peri-implant structures, this soft tissue barrier, supracrestal soft tissue attachment, must be formed.[7] Various factors determine the amount of biological width in periimplant tissues, such as the surface properties of the implant, their design, and loading protocols. The amount of crestal bone loss that occurs during the development of the biological width is determined by these variables, which are typically related to the quality of the mucosal seal.[6]

The structure of the peri-implanter soft tissue has been studied in various human and animal researches. In a study conducted on dogs by Berglundh et al. in 1991, characteristics of the gingiva around the teeth and anatomical characteristics of the mucosa around the implant are compared. It is seen that the color of clinically healthy gingiva and peri-implanter mucosa is dusty rose pink. When radiographs are examined, it was determined that alveolar bone level on the dentated area is on the 1 mm apical of cement-dentin con-

nection. It was determined that marginal bone crestal is close to implant-abutment connection.[4,8]

Histological studies have shown that peri-implanter and periodontal soft tissues have common characteristics. The gingival epithelium is finely keratinized and continues with a thin connection epithelium on the surface facing the dentin, ends on the dentin-cement connection. Supraalveoler connective tissue is at a level of approximately 1 mm, and the width of the periodontal ligament is 0.2-0.3 mm. External of the peri-implanter mucosa is covered with a keratinized epithelium continuing with a thin barrier epithelium on the marginal side. This barrier epithelium has a thickness of several cell layers and ends at the 2 mm apical of the soft tissue margin. The titanium oxide surface of the implant is in direct contact with the connective tissue on the bone. This connective tissue contains collagen fibers. Collagen fibers are rooted from the periost of alveolar bone crestal and go parallelly towards the abutment surface of the soft tissue margin. Periodontal epithelium and peri-implanter epithelium take root on the dens/implant surface with hemidesmosomes.[4]

In a healthy mucosa, the barrier epithelium should be in a coronal position of 1-1.5 mm from the level of the alveolar bone. Connective tissue-based fibroblasts of the mucosa generate a connection to the titanium oxide surface in the apical of abutment part in the post-implant-surgery recovery period.[4]

Even though Abrahamson et al. used different types of implants in the studies they held on dogs in 1996 and 2002, they have shown that similar mucosal attachments will form. Also, it was shown that attachment formation is an independent process from whether the implant is submerged or not.[9,10]

Epithelium and connective tissue components around the transmucosal attachment of implant are important for wound healing. This wound healing happening after the implant has been placed, is a sore process including a several-week tissue remodeling. In other words, the formation of the transmucosal attachment is essential in wound healing success in the post-surgery process.[4]

Peri-implanter soft tissue quality

In a study conducted by Berglundh et al. in 1991, dens and connection tissues around the implant had been examined. They said that the most important difference in the mesenchymal tissues around the dens and implant is the cement formation around the root. Cement-based thick dentoalveolar and dentogingival fiber bundles around the natural teeth come in lateral, coronal and apical directions. Processes of the collagen fibers around the implant; however, are totally different. Collagen fibers rooted from the periosteum of bone crestal go parallelly towards the implant surface. And some of the fibers are seen as bundles on the far areas from the implant surface.[4,8]

There are more collagen fibre substances in the connective tissue around the implant than natural teeth. Again, they contain less fibroblast and vascular element. Moon et al. determined in a study conducted in 1999 that there are only a couple of blood vessels around the implant. Various fibroblasts have been found throughout the implant's long centerline. It was seen that when the lateral components of the implant increase, fibroblast number decreases and collagen fibre and vascular structure increases. Studies similar to Moon et al.'s study have found the same results and it was concluded that the connective tissue around the implant is fibroblast rooted.[4,11]

Gingiva blood build-up in teeth occurs from two main sources. One of them is supraperiosteal blood vessels, and the other one is periodontal ligament-based vascular plexus. Blood build-up in the peri-implanter tissues has been examined on dogs by Berglundh et al. in 1991. The main source of blood build is shown as the supraperiosteal blood vessels on the bone. These vessels vein in the supraalveolar mucosa, form capillary vessels under the oral epithelium, and vascular plexus in the lateral of barrier epithelium. The connective tissue of the transmucosal attachment contains only a couple of blood vessels. All of these vessels can be named as the terminal veins of the supraperiosteal blood vessels. In other words, they show differences in the blood build-up point although periodontal soft tis-

sues share various characteristic features.[4] Despite the fact that osseointegrated implants can be successfully maintained over time, the presence of periimplant mucosal recessions can have a significant impact on esthetic outcomes, patient satisfaction, as well as biological and clinical stability, all of which are important factors for a long-term good prognosis.[12] The inability of soft tissue around the implant compromises esthetics, especially in the interproximal papillary and facial aspects. In addition, in cases where the soft tissue is improved by grafting methods, it has been reported that periimplanter clinical parameters such as bleeding on probing and probing depth are better.[13] Anatomic and prosthetic aspects both play a role in the successful modeling of soft tissues. To ensure soft tissue responsiveness to prosthetic stimuli, an adequate blood supply must first be provided, followed by an appropriately linked and positioned abutment, which serves as the foundation for a well-designed interim prosthetic component.[14] At this point, it seems that ensuring the correct organization of the soft tissue around the implant is very critical for maintenance of dental implants.

Soft tissue grafts and membranes

Soft tissue grafts have been used for many years in the reconstruction of crest defects and in gingival recession.[15] Also, soft tissue thickness was increased in some studies where autogenous and allogenic grafts were used to prevent early period marginal bone loss.[16,17] Compared to the areas with thin mucosa, when mucosa was thickened with membranes on the areas where soft tissue thickness is 2 mm or less, a statically meaningful less marginal bone loss was observed.[16,17]

Sizes of the defect determine the used method and graft type. As a basis, grafts divide into two as free and pedicle grafts on the augmentation of soft tissues; free soft tissue grafts and pedicle soft tissue grafts.[11]

The connection of the graft with the donor site is completely cut off on free soft tissue grafts. Free gingival graft, connective tissue graft, interpositional grafts, onlay grafts, onlay-interpositional graft combination and noncellular dermal matrix application are the methods used in soft tissue augmentation. The connection of the graft with the donor site is not cut off on pedicle soft tissue grafts. Defected adjacent area or palatal area can be used as the donor site. Roll method or vascularized interpositional periosteal connection tissue graft technique are frequently used in soft tissue augmentations.[18]

Amount of keratinized mucosa

In a study conducted by Bengazi et al. on five dogs in 2013, according to the examination results of implant and peri-implanter tissues, more bone resorption was observed in the implants surrounded with alveolar mucosa than the ones surrounded with keratinized mucosa.[19] According to a review made in 2012, it was concluded that the effects of the presence or absence of keratinized mucosa are limited to providing tissue stability. Half of the analyzed journals say that plaque score and the bleeding index were observed in individuals who have keratinized mucosa less than 2 mm, 8 of 10 reports have shown that there is no meaningful difference in the probing depth.[20] In clinical practice, a keratinized tissue width of ≥ 2 mm is considered adequate, and a width of < 2 mm is considered inadequate. The accepted knowledge is that adequate keratinized tissue will improve plaque control in the region and provide optimum aesthetics. However, there is no consensus on the effect of the width of the keratinized tissue on the health of the periimplant tissues.[21] In the study of Bouri et al. on 200 implants, the relationship between keratinized mucosal width and peri-implant bone loss was investigated. According to the results of the study, an increase in the width of the keratinized mucosa around the implant indicates less soft tissue inflammation and less marginal bone loss.[22] The results of a more recent clinical trial published by Shimomoto et al. in 2021 also suggest that the width of keratinized tissue increases periimplant bone stability.[23] On the other hand, Roccuza et al., in their retrospective study published in 2015 with 10 years of follow-up, concluded that even if the width of

the keratinized tissue is inadequate, this condition can be tolerated with good oral care.[24] According to the study of Kim et al. in 2009, inadequate keratinized tissue width around the implant does not have a definite negative effect on poor oral hygiene and soft tissue health. However, in the same study, it was added that the lack of keratinized tissue has an effect on gingival recession and marginal bone loss.[25]

Peri-implanter mucosal thickness and marginal bone loss

In 1996, Lindhe and Berglundh showed in the study they have conducted that keratinized mucosa thickness affects the bone stability around the implant. With this study, implant success and the importance of soft tissue thickness in protecting marginal bone were determined.[10] Based on this data, soft tissue thickness's effect on bone stability around the implant has been analyzed. Linkevicius et al. examined the effect of mucosal thickness on marginal bone loss on 26 patients and 65 implants in 2009. In the study, 32 implants were placed as 2 mm supra-crestal, and the other 32 were placed as bone level. Mucosal thicknesses were classified as thin, medium and thick. Crestal bone changes were measured at the end of a one-year follow-up. On average, the thin mucosa showed bone loss of 1.35 mm, medium mucosa 0.32 mm and thick mucosa of 0.12 mm. It has been concluded that initial mucosa thickness may affect the amount of crestal bone loss in implants placed as supracrestal form.[26] In another study by the same researchers, the mucosal thicknesses of the implant-placed regions are divided as more than 2.5 mm and less than 2.5 mm. Nine implants are placed in thin mucosal areas, and 14 implants are placed in thick mucosal areas as 2 mm supracrestal. 23 implants were placed as control groups on the crestal level. The measurements found that the marginal bone loss in the thin mucosa was more than the thick mucosa. It is also stated by the researcher that supracrestal implant placement should be avoided in areas of thin mucosal thickness.[27] Similarly, in a 2-year follow-up study on 79 edental patients in 2012 by Vervaeke et al. that there may be more marginal bone loss in patients or areas with insufficient soft tissue.[28]

In 2014, Linkevicius et al. studied the effects of soft tissue thickness on marginal bone change in implants with platform-switch design. In the study where 80 bone-level implants are used, the areas to be implanted are divided into two groups as thin (less than 2 mm) and thick (2 mm or more), depending on the mucosa thickness. On the marginal bone measurements at the end of 1 year, a loss of bone of 1.17 mm in thin mucosal thickness and 0.21 mm in thick mucosal thickness was seen. Depending on the measurements, researchers concluded that the platform switch implant-abutment connection design will not be sufficient to maintain the crestal bone level in individuals with a thin mucosal biotype. The use of platform-switch design in individuals with thick mucosal biotype is said to have significantly reduced bone loss.[29]

It was examined by Weisner et al. in 2010 to see if the thickening of soft tissue by augmentation could have an effect on marginal bone loss. After 12 months of follow-up, the average marginal bone loss in soft tissues where augmentation was applied was determined to be 0.8 mm and 0.6 mm in non-applied regions.[16] In 2020, Puzio et al. conducted a study on patients with implant indication on mucosal regions by applying soft tissue augmentation again. For augmentation, xenogenic collagen matrix or connective tissue graft were used. Patients who have undergone a soft tissue augmentation procedure are also divided into subgroups based on the application being performed before or after implantation. In the 12-month follow-up period study, 0.5 mm bone loss was observed in the thin mucosal and non-augmented patient group, while the loss was recorded as 0.4mm in the group with soft tissue augmentation connective tissue graft and pre-implanted. According to the results of this study, increased thickness of soft tissue was associated with less marginal bone loss.[17]

In a retrospective study conducted by Burschi et al. in 2014 on 120 patients and 135 implants, all implants

were placed in areas where the mucosal thickness was 3.0 mm. 1.20 mm bone loss was observed after 1 year of follow-up, while at the end of the 3rd year, 1.09 mm bone gain was realized.[30]

Jeong et al. conducted a prospective study in 2011 on 241 patients and 432 implants. In the study, the mucosal thickness was divided into two as less than 3.0 mm and more than 3.0 mm. 318 implants were located in areas with less than 3.0 mm mucosal thickness, and 114 implants were located in areas with 3.0 mm and more thickness. The marginal bone loss in the thin mucosa was found on average 0.3 ± 0.2 mm and 0.3 ± 0.6 mm in thin mucosa after 1 year of follow-up. There was no significant difference between the two groups as marginal bone loss amounts.[31]

The study conducted by Canullo et al. in 2017, compared the marginal bone loss of the areas covered with thick and thin mucosa after 1st and 3rd year. While thin mucosa showed a loss of 0.27 mm at the end of the 1st year and 0.35 mm at the end of the 3rd year, the end of the 1st year in the thick mucosa was calculated as 0.17 mm and 0.11 mm on the 3rd year.[32]

In the study conducted on 70 patients and 70 implants in 2019, Spinato et al. examined the effect of both mucosal thickness and abutment height on bone loss. After 12 months of follow-up time, they observed bone loss of 0.67 mm in 1 mm abutment usage, 0.35 mm in 3 mm abutment usage in thin mucosa; and a bone loss of 0.70 mm in 1 mm abutment usage, 0.33 mm in 3 mm abutment usage in thick mucosa.[33]

Pazmino et al. followed the 12-months bone loss in thin and thick mucosa on a total of 26 patients in 2020. In the final radiographic measurements, a bone loss of 1.7 mm in thin mucosa and 1.59 mm in thick mucosa was measured.[24]

In 2021, Gharpure et al. examined the effects of mucosal thickness on the development of peri-implantitis on 63 patients and 195 implants. In the study with a follow-up period of 6.9 ± 3.7 years, perimplantitis and periimplant mucositis were detected at a higher rate in implants placed in thin mucosa. In the study, where the focal point is not a marginal bone loss but also radiographic data is analyzed, marginal bone loss in the fine mucosa was higher than the thick mucosa, but the difference between them was not statistically significant.[35]

Discussion

Dental implants are seen as materials that can mimic the root of the teeth as close to natural as possible.[1] They provide to eliminate the many disadvantages of tooth-supported stable and removable prostheses. In addition to their advantages, the maintenance of dental implant treatments and their ability to maintain their functions with health can be considered a common concern in many branches of dentistry. A successful dental implant and implant conformation represent different clinical tables. Implant conformation refers to the presence of the dental implant in the mouth.[26] In the past 20 years, many studies have been conducted by researchers, clinicians and implant manufacturers to improve dental implant success. The risk factors that have been effective in dental implant losses and failures have been investigated.

Alberktsson et al. have been diagnosed the periimplantitis at a rate of 2.7% in the 10-year follow-up of modern implants in their study published in 2017. With the aim of increasing the success of implant treatment, reducing or preventing early marginal bone loss has been the focus of our study. Marginal bone loss is examined in the early and late periods. Bone loss seen in the first 1 year is a treatment complication and is usually aseptic. Marginal bone loss seen after the first year is about pathology.[37] Factors that cause marginal bone loss include premature loading, micro-spacing formation, infection, traumatic surgery, cement residue around implant-top prosthetics, reorganization of biological range and soft tissue thickness.

A gap of micron width occurs in the connection caused by the healing head or abutment on the implants placed. This gap, which is inevitably occurring, has been shown to be associated with marginal bone loss and inflammatory cell infiltration.[38,39] The contact or proximity of the micro-range to the crestal bone trig-

gers marginal bone repression. Therefore, it is recommended that two-stage implants are not positioned below 1 mm or 1 mm bone level.[30]

The effect of the platform-switch implant abutment design on marginal bone loss is a highly researched topic. However, the studies have not been combined at a common point, and there are conflicting results. Lazzara and Porter used large implants and narrow-sized abutments and radiologically monitored marginal bone conditions in their study in 2006. They said that the marginal bone was better preserved than the horizontal-match implant-abutment connection design as a result of the follow-up.[41] The multiple studies on this new implant-abutment connection concept have not found a statistically significant difference if the mucosal thickness is less than 2 mm.[42,43]

Linkevicius et al. said that the platform switch implant-abutment design may not produce a successful result in thin mucosa in their study published in 2010. In the study using a total of 12 implants, six implants were selected as platform-switch and six implants were selected as horizontal-match. All implants were placed in a thin mucosa of 2 mm or less, and there was no statistically significant difference between the measurements made in the two groups.[44] In a study conducted by the same researchers in 2014, the platform switch implant-abutment connection design was implemented in individuals with different mucosal thicknesses. In the study where 80 bone-level implants are used, the areas to be implanted are divided into two groups as thin (less than 2 mm) and thick (2 mm or more), depending on the mucosa thickness. Depending on the radiological measurements, researchers concluded that the platform switch implant-abutment connection design will not be sufficient to maintain the crestal bone level in individuals with a thin mucosal biotype. The use of platform-switch design in individuals with thick mucosal biotype is said to have significantly reduced bone loss.[29] In both studies conducted by the same researchers, the history of periodontitis, cigarette habit, diabetes, alcoholism and the use of medication to retard wound recovery were eliminated in the selection of patients. To say that the platform-switch design will not work in thin mucosa, longer-lasting follow-up and further research are needed. Furthermore, it is not possible to generalize the statistical result obtained because the number of implants followed is very small. A more recent study of Puzio et al. using 75 platform-switch implants in 2020 can actually be interpreted in a similar way. The study evaluated 1 year of marginal bone loss in cases of soft tissue augmentation has applied and not applied. In the group with soft tissue augmentation before implantation, statistically less marginal bone loss was detected than the group with thin mucosa and no soft tissue augmentation. It is possible to read these results through thin mucosa as platform-switch design cannot provide superior or equal to platform-switch design with thick mucosa.[31]

There are some limitations that prevent us from accepting the potential impact in most of the studies when the current literature on the effect of initial soft tissue thickness on marginal bone loss is examined. Many of the studies in the current literature contain heterogeneity. The inclusion and exclusion criteria may have caused patient selection bias. It is not possible to generalize the results to the entire community, especially because diabetes, cigarettes and periodontitis are the exclusion criteria in many studies. Because most of the work that meets the inclusion criteria is the same, the possibility of taking sides increases. The fact that most of the work in the literature has been done by the same researcher reduces objectivity to the subject. In addition, marginal bone loss was evaluated only as mesial and distal, and no facial and lingual bone loss assessment was performed. However, the loss of bone around the implant can affect all surfaces.

Studies with the longest follow-up period in the literature are the studies of Canullo et al. in 2017 and Bruschi et al. in 2014. In both studies, radiographic bone changes were followed for 3 years.[30,32] Other than these studies mentioned, the published studies were on average based on 12 months of data. Studies with longer follow-up times are needed to ensure the effectiveness of the mucosal thickness on marginal bone loss.

Conclusion

» Mucosal thickness is seen as not only a provider for aesthetic and plaque control around the implant but also as a possible factor to prevent marginal bone loss.

» Studies with a longer follow-up period, examined on larger populations or multicenter researches are needed for more accurate results.

» Clinical effects of the studies which show differences and say that mucosal thickness is an efficient factor on marginal bone loss around the implant are argumentative.

» It should not be forgotten that osteonecrosis around the implant is a multifactorial and complex process, and it is not possible to tie it with one clinical condition. Inclusion and exclusion criteria in the following studies should be determined in view of these factors.

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Drafting the manuscript or revising the content: BY, MT

Final approval of the version to be published: BY, MT

Table 1. Original articles investigating the effect of soft tissue thickness on peri-implant bone loss between 2009 and 2020

Article	Mucosal thickness	n	Implant number	Control group	Test group	Follow-up period	MBL
Linkevicius 2009	<2.5 mm ≥2.5 mm	19	thin: 9 thick: 14 (23 control)	bone-level	2 mm supra-crestal	12 months	thin: 1.45 mm thick: 0.2 mm
Linkevicius 2009	thin: ≤2 mm medium: 2.01-3.00 mm thick: ≥ 3 mm	26	12 12 12 12 8 8	bone-level	supra-crestal	12 months	thin: 1.35 mm medium: 0.32 mm thick: 0.12 mm
Linkevicius 2010	<2 mm	10	control: 6 test: 6	horizontalmatch	platform-switch	12months	control: 1.6 test: 1.79
Jeong 2011	<3 mm ≥3 mm	241	318 114	thick mucosa	thin mucosa	12 months	0.3 ± 0.2 0.3 ± 0.6
Linkevicius 2013	A: <2 mm B: 2 mm +membrane C: ≥2 mm	103		thick and thin +membrane	thin mucosa	12 months	A: 1.65, 1.81 B: 0.31, 0.34 C: 0.44, 0.47
Linkevicius 2013	T1≤2 mm T2≥2 mm C <2 mm + membrane	97	33 32 32	thin+membrane	thin mucosa	12months	T1: 1.22,1.14 T2: 0.24,0.2 C: 0.22,0.2
Linkevicius 2014	<2 mm ≥2 mm	80	40 40	thick mucosa	thin mucosa	12 months	1.17 0.21
Linkevicius 2015	≤2 mm	30	30: PS 30: LM	laser micro.	platform switch	12 months	L.M.: 1.41 P.S.: 1.43
Van Eekeren 2015	A: 2 mm or less B:more than 2 mm	33	A: k: 17 sk: 15 B: k: 20 sk: 22	2.5 mm supra	crestal	12 months	Crestal A: 0.6 ± 0.5 B: 0.2 ± 0.4
Bhat 2015	<2 mm ≥2 mm	20	33	thick mucosa	thin mucosa	12 months	thin: 1.70 ± 0.36 thick: 0.61 ± 0.36

Table 1. Continued

Article	Mucosal thickness	n	Implant number	Control group	Test group	Follow-up period	MBL
Puzio 2020		57	75	15 Implants (without augmentation) GROUP-I	15 Implants (pre-implantation augmentation) GROUP-II 15 Implants (post-implantation augmentation) GROUP-III	12 months	Group-I: 0.5 mm Group-IIa: 0.6 -0.7 mm Group-IIb: 0.4 mm Group-IIIa: 0.5 - 0. 6mm Group-IIIb: > 1.0 mm
Pazmino 2020	thin ≤2.0 mm thick >2.0mm	26	thin: 13 thick: 13	thick mucosa	thin mucosa	12 months	thin: 1.7 mm thick: 1.59 mm
Weisner 2010	with augmentation: 3.20 mm Control: 1.9 mm	10	test: 10 control: 10	without augmentation	with augmentation	12 months	with graft: 0.8 mm with no graft: 0.6 mm
Spinato 2019	thin ≤2.0 mm thick >2.0 mm	70	70	thick (B1 - B3)	thin (A1 - A3)	12 months	A1: 0.67 ± 0.11 A3: 0.35 ± 0.09 B1: 0.70 ± 0.10 B3: 0.33 ± 0.05
Bruschi 2014	thick: 3.0 mm	120	135			3 years	1st year: -1.20 ± 0.41 3rd year: +1.09 ± 0.38
Canullo 2017	thin ≤2.0 mm thick >2.0 mm	26	68	thick	thin	3 years	thin -> 1st year: 0.27 3rd year: 0.35 thick -> 1st year: 0.17 3rd year: 0.11

n, Number of patients

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Effects of systemic isotretinoin treatment on retinal nerve fiber layer thickness and corneal endothelial cell density

Sistemik izotretionin tedavisinin retina sinir lifi tabakası kalınlığı ve kornea endotel hücre yoğunluğu üzerindeki etkileri

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Abstract

Objective To investigate the effects of systemic isotretinoin therapy on retinal nerve fiber layer (RNFL) thickness and corneal endothelial cell density (ECD)

Methods Thirty-three patients completed the study. All patients were given an ophthalmic examination at baseline and after six months of isotretinoin therapy. All patients underwent a detailed eye examination including best corrected visual acuity, intraocular pressure, refractive errors, biomicroscopic anterior segment and fundus examination. In addition, Schirmer test without topical anesthesia, tear break up time, retinal nerve fiber thickness measurements with optical coherence tomography (OCT) and specular microscopy measurements were performed on all patients.

Results There were 23 female (69.7 %) and 10 male (30.3 %) patients. Post treatment RNFL values were significantly lower than pretreatment values on both right and left eyes (P=0.048 and P<0.001). We did not find any correlation between total dose of isotretinoin and mean RNFL thickness values on both right and left eyes (P=0.118, P=0.909). There were no significant differences in the mean Schirmer scores, Break up time values of both eyes during the treatment compared with the baseline values. There were significant differences in corneal ECD between pre and postreatment period (P=0.017, P=0.006).

Conclusion After the use of oral isotretinoin for six months, we found decreased RNFL and CCT thickness by OCT.

Key words: *isotretinoin, eye, cornea, retina*

Öz

Amaç Sistemik izotretinoin tedavisinin retina sinir lifi tabakası (RSLT) kalınlığı ve kornea endotel hücre yoğunluğu

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üzerindeki etkilerini değerlendirmek.

Yöntem Otuz üç hasta çalışmayı tamamladı. Tüm hastalara başlangıçta ve tedavi süresince tedavinin başlangıcından altı ay sonra oftalmik muayene yapıldı. Tüm hastalara düzeltilmiş görme keskinliği, göz içi basıncı, kırma kusurları, biyomikroskopik ön segment ve fundus muayenesini içeren detaylı bir göz muayenesi yapıldı. Ayrıca tüm hastalara topikal anestezi yapılmadan Schirmer testi, gözyaşı kırılma zamanı bakıldı, optik koherens tomografi ile retina sinir lifi kalınlık ölçümleri ve speküler mikroskopi ölçümleri yapıldı.

Bulgular 23 kadın (%69.7) ve 10 erkek (%30.3) hasta dahil edildi. Tedavi sonrası RSLT kalınlığı hem sağ hem de sol gözde tedavi öncesi değerlerden anlamlı derecede düşüktü (P=0.048 ve P<0.001). Hem sağ hem de sol gözde toplam izotretinoin dozu ile ortalama RSLT kalınlık değerleri arasında herhangi bir ilişki bulunamadı (P=0.118, P=0.909). Tedavi sırasında her iki gözün ortalama Schirmer skorları, kırılma zamanı değerlerinde başlangıç değerleriyle karşılaştırıldığında anlamlı bir fark yoktu. Kornea endotel hücre yoğunluğunda tedavi öncesi ve sonrası dönem arasında anlamlı farklılıklar vardı (P=0.017, P=0.006).

Sonuç Altı ay süreyle oral izotretinoin kullanımı sonrası OKT ile RSLT ve kornea kalınlığında azalma saptadık.

Anahtar kelimeler: *izotretinoin, göz, kornea, retina*

Introduction

Oral isotretinoin was approved by the FDA in 1982 for the treatment of severe acne. It is the first-line treatment choice in severe acne vulgaris. Isotretinoin is the only drug that can be effective on all the factors that are valid in acne vulgaris pathogenesis.[1]

There are many side-effects of oral isotretinoin treatment, most commonly dose-dependent side-effects include cheilitis, dermatitis, facial erythema, xerosis, mucositis, epistaxis, conjunctivitis and blepharitis; the majority of these can be predicted and do not require treatment termination.[1] The majority of ocular side-effects are meibomian gland atrophy, impaired meibomian gland secretion, blepharoconjunctivitis, dry eye, keratitis, myopia, decreased color vision, optic neuritis, diplopia, optic disc edema and idiopathic intracranial hipertansiyon.[2,3] In a retrospective study Brzesinski et al., showed that the frequency of ocular side effects was 8.96% and the most common side effect was dry eye disease (5.7%) in 3525 patients who received isotretinoin treatment (0.2-0.5 mg/kg/day).[4]

Good visual acuity requires a transparent cornea which is essential for the formation of a clear image on the retina. The corneal endothelium has both barrier and pump functions, which are important for the maintenance of corneal clarity. The RNFL of the retina contains the non-myelinated axons of the retinal ganglion cells that form the optic nerve. The measurement of retinal nerve fiber layer (RNFL) thickness is a valuable tool for demonstrating early retinal damage.[4,5]

Recently with the introduction of optical coherence tomography devices, noninvasive and objective imaging has been used frequently. In a study Ucak et al. determined that there was focal thinning in the retinal nerve fiber layer in patients using isotretinoin.[5] Sekeryapan et al. reported that there was no change in the nerve fiber layer and ganglion cell layer in 28 patients using isotretinoin.[6] Although some of the side effects associated with the use of isotretinoin are well established, there are not many publications in the literature on changes and damage in the anatomical structures of the eye.

In this study, we aimed to contribute to the literature by evaluating retinal nerve fiber thickness and corneal endothelial cell density changes that may develop in the eye due to isotretinoin treatment.

Methods

Fifty patients with acne vulgaris were enrolled into this observational study. Patients' pretreatment demographic and clinical characteristics (age, gender, follow-up time, total dose of isotretinoin) were recorded. All of the patients were treated for acne with

systemic isotretinoin in total dosages of at least 0.3-0.5 mg/kg /day for a period of six months. Thirty-three patients completed the study.

All patients were given an ophthalmic examination at baseline and during the treatment, six months of the start of the treatment. All patients underwent a detailed eye examination including best corrected visual acuity, intraocular pressure, refractive errors, biomicroscopic anterior segment and fundus examination. In addition, Schirmer test without topical anesthesia, tear breakup time, retinal nerve fiber thickness measurements with optical coherence tomography and specular microscopy measurements were performed on all patients.

The study was approved by the Local Ethics Committee of Karadeniz Techinical University School of Medicine and has been conducted in accordance with the guidelines for human studies and Declaration of Helsinki. Informed consent was obtained from all subjects.

High myopia or hyperopia (>6.00 D), corneal astigmatism >2.5 D, axial length greater than 26 mm and shorter than 22 mm, any known ocular disease (glaucoma, ocular hypertension, uveitis, cornea pathology), a history of ocular surgery, a history of contact lens use, and those who could not comply with any of the measurement methods were not included in the study. Intraocular pressure measurements were made with a non-contact tonometer device (Nidek NT-530, Japan). Schirmer test was performed without applying topical anesthesia to the patient. Filter papers (Whatman filter paper, Optitect) measuring 5x35 mm were placed in the conjunctival fornix on the outer 1/3 of the patient's lower lid. The patient was asked to blink as necessary and close the eye. After five minutes, the amount of wetness was measured and evaluated. Values below 10 mm were evaluated in favor of aqueous tear insufficiency.

To measure the tear breakup time (BUT), fluorescein drops were instilled into the lower fornix without the use of topical anesthetics. Fluorescein was spread by asking the patient to blink 3-4 times. The tear film was examined in a slit-lamp microscope with wide illumination using a cobalt blue filter. The time from the last blink to the first dry spot was determined. The measurement was repeated three times and averaged, and the measurement of this value below ten seconds was considered pathological.

Specular microscopy was performed with the non-contact specular microscopic measurement NIDEK (CEM-530) device. While measuring, it was noted that the highest quality image was obtained. With the measurement, endothelial cell density (ECD), central corneal thickness (CCT) were calculated. OCT measurements were made with the Optovue RTVue (RT 100, software version 6.3, Optovue, Fremont, CA) device. Peripapillary RNFL was placed on the optic disc head with a 3.4 mm scanning diameter ring around it and mean inferior, superior, nasal and temporal thickness measurements were made. All measurements were made by the same technician.

Statistical analysis

Data analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). The normality of the data was confirmed using a Kolmogorov-Smirnov test. A paired t test was used to compare the study measurements at the baseline and at follow-up visits. Mann Whitney U test was performed for non-normally distrubited data. The correlation analysis between the mean RNFL score, the total dose of isotretinoin were analysed using Pearson's correlation tests. Differences with a value of $P<0.05$ were considered to be statistically significant.

Results

Demographic data

There were 23 female (69.7 %) and 10 male (30.3 %) patients. Mean age was 19.80 ± 5.70 years, with a range of 13-44 years. The mean daily dosage of isotretinoin was 29.09 ± 6.10 mg, mean follow up time of the drug use was 6.36 ± 0.80 months. The total dose of isotretinoin was 7345 ± 1084 (5400-9000) mg. The severity of acne was moderate in 16 patients (48.5%) and severe in 17 (51.5%).

Differences between the baseline and during the treatment

The relationship between ocular changes in all eyes at the baseline and during the treatment is summarized in Table 1.

Before and after treatment, a complete ophthalmologic examination was normal in all eyes.

There were no significant differences in the mean Schirmer scores, BUT values of both eyes during the treatment were compared with the baseline values. Post treatment RNFL values were significantly lower than pretreatment values on both right and left eyes ($P = 0.048$ and $P<0.001$). We did not find any correlation between total dose of isotretinoin and RNFL values on both right and left eyes ($P=0.118$, $P=0.909$).

The BUT values were 8.20 ± 2.80 in the right eye at the beginning of the treatment, 7.80 ± 2.40 in the 6th month of the treatment, 8.40 ± 2.80 in the left eye at the beginning of the treatment and 7.60 ± 2.20 in the 6th month of the treatment. No statistically significant

Table 1. Averages of the RNFL thickness, Corneal Endothelial Cell Density, BUT values and Schirmer test scores before and during the treatment

Tests (mean +-SD)	Baseline	Sixth month	*P* value
TO right	15.00 ± 3.30	14.30 ± 2.30	0.377
TO left	15.10 ± 2.80	14.10 ± 2.70	0.202
CD right	2768.64 ± 172.40	2683.70 ±262.94	0.125
CD left	2821.30 ± 282.70	2744.48 ±262.89	0.257
RNFL right	108.71 ± 7.470	105.08 ± 7.16	**0.048**
RNFL left	109.75 ± 9.48	101.99 ± 6.75	**<0.0001**
RNFL superior right	130.10 ± 12.42	110.00 ± 11.40	**<0.0001**
RNFL superior left	129.80 ± 20.44	113.43 ± 12.30	**0.004**
RNFL inferior right	128.60 ± 15.62	109.59 ± 9.03	**<0.0001**
RNFL inferior left	124.60 ± 13.61	108.47 ± 9.89	**<0.0001**
RNFL temporal right	81.90 ± 12.53	78.40 ± 18.43	0.581
RNFL temporal left	80.43 ± 13.98	71.40 ± 7.82	0.061
RNFL nasale left	81.23 ± 11.34	78.90 ± 18.43	0.555
RNFL nasale right	79.37 ± 18.35	75.70 ± 9.15	0.550
CCT right	591.91 ± 40.31	555.37 ± 26.41	**0.017**
CCT left	589.27 ± 36.21	553.84 ± 29.02	**0.006**
BUT right	8.20 ± 2.80	7.80 ± 2.40	0.545
BUT left	8.40 ± 2.80	7.60 ± 2.20	0.227
Schirmer right	13.10 ± 6.90	13.60 ± 6.40	0.757
Schirmer left	13.70 ± 6.90	14.20 ± 5.60	0.740

difference was observed in terms of BUT values at the beginning and end of the treatment (P>0.05). The mean Schirmer test scores in the right eye was 13.10 ± 6.90 at the beginning of the treatment, it was 13.60 ± 6.40 in the 6th month. The mean Schirmer test in the left eye was 13.70 ± 6.90 at the beginning of treatment and 14.20 ± 5.60 at the 6th month of treatment. There was no statistically significant difference in terms of Schirmer test scores at the beginning and end of the treatment (P>0.05).

While the mean corneal ECD in the right eye was 2768.64 ± 172.40 cells/mm^2 at the beginning of treatment, it was 2683.70 ± 262.94 cells/mm^2 at the 6th month of treatment. The mean corneal ECD in the left eye was 2821.30 ± 282.70 cells/mm^2, it was 2744.48 ± 262.89 cells/mm^2 at the 6th month of treatment. No statistically significant difference was observed in terms of corneal ECD at the beginning and end of the treatment (P>0.05).

The mean retinal nerve fiber thickness (RNFL) in the right eye was 108.71 ± 7.47 µm at the beginning of treatment and 105.08 ± 7.16 µm at the 6th month of treatment (P=0.048). The mean RNFL was 109.75 ± 9.48 µm in the left eye and 101.99 ± 6.75 µm at six months of treatment (P<0.0001). Superior RNFL thickness was 130.10 ± 12.42 µm at the beginning of treatment in the right eye, and 110.00 ± 11.40 µm at the 6th month of treatment (P<0.0001). Superior RNFL thickness in the left eye was 129.80 ± 20.44 µm at the beginning of treatment and 113.43 ± 12.30 µm at the 6th month of treatment (P=0.004). Inferior RNFL in the right eye was 128.60 ± 15.62 µm at the beginning of treatment and 109.59 ± 9.03 µm at the 6th month of treatment (P<0.0001). Inferior RNFL in the left eye was 124.60 ± 13.61 µm at the start of treatment and 108.47 ± 9.89 µm at six months of treatment (P<0.0001). There was no statistically significant difference in terms of temporal and nasal RNFL thickness in the right and left eyes at the beginning of treatment and at the sixth month of treatment (P>0.05).

CCT was 591.91 ± 40.31 µm in the right eye at the beginning of treatment and 555.37 ± 26.41 µm at the 6th month of treatment (P=0.017). CCT in the left eye was 589.27 ± 36.21 µm at the beginning of treatment and 553.84 ± 29.02 µm at the 6th month of treatment (P=0.006).

Discussion

Ocular side effects of systemic isotretinoin were encountered with moderate frequency. Most ocular side effects associated with oral isotretinoin use are dose dependent. Ocular side effects of isotretinoin are meibomian gland atrophy, impaired meibomian gland secretion, blepharoconjunctivitis, dry eye, keratitis, myopia, decreased color vision, optic neuritis, diplopia, optic disc edema.[2,3]

In our study, we found that mean, superior and inferior RNFL thickness decreased in both eyes at the end of the 6-month follow-up period. In the literature, studies investigating the effects of isotretinoin treatment on RNFL thickness show different results. Kapti et al.[7] found no significant difference in RNFL thickness in the 6-month follow-up of patients who received systemic isotretinoin treatment compared to pretreatment. Sekeryapan et al.[6] examined the changes in RNFL and ganglion cell complex in patients receiving 1 mg/kg/day oral isotretinoin treatment and reported that systemic isotretinoin treatment had no negative effect on RNFL thickness and ganglion cell complex. Similarly, Bakbak et al. showed that isotretinoin did not cause a statistically significant change in peripapillary RNFL thickness or visual field findings within the usage period, and within three months after cessation. Karadag et al[9] reported that after the use of oral isotretinoin for three months, no significant side effects were observed in choroidal thickness, CMT, and RNFL thickness by OCT.

Unlike these studies; Yilmaz et al.[10], observed that the RNFL thickness in the temporal quadrant was significantly lower at baseline, 1st, 2nd and 3rd months compared to baseline, and no significant change was observed in the other quadrants. Ucak et al.[5] measured RNFL subjects receiving oral 0.5-2 mg/kg/day oral isotretinoin treatment and found a thinning in the inferior temporal quadrants. In our study RNFL

thinning in the superior and inferior quadrants of both eyes were detected, however not in temporal and nasal quadrants.

Some studies have shown that systemic isotretinoin treatment has no effect on Schirmer scores.[11,12] Yildirim et al. applied Schirmer test without anesthesia and Schirmer test with topical anesthesia before treatment, at 1, 3, 6 months and 6 months after the end of treatment to 54 patients who were taking isotretinoin. There was no significant change in the Schirmer test without anesthesia, and a statistically significant decrease was observed in the Schirmer test with topical anesthesia during the treatment compared to the pretreatment.[13] In our study, no statistically significant difference was observed in the mean non-anesthetic Schirmer test measurements before the treatment and at the sixth month after the treatment.

In our study, no statistically significant difference was observed in the number of corneal endothelial cell density before and after the 6-month follow-up with systemic isotretinoin treatment. In our study, significant change was observed in CCT measurements at the 6th month of treatment compared to pre-treatment. Similarly, Yuksel et al. investigated the changes in CCT and Meibemoim gland disease score severity in 47 patients receiving systemic isotretinoin therapy.[14] A significant change was observed in CCT measurements at the 6th month of treatment compared to pre-treatment. In addition, it was determined that CCT values and the severity of Meibemoim gland disease showed a negative correlation at the 6th month of the treatment. Similarly, Cumurcu et al. reported that CCT decreased at the 6th month after systemic isotretinoin treatment compared to the pre-treatment level.[15]

Conducting the study with a small number of patients, evaluating the short-term data, the limitations of our study. More detailed information can be obtained with new studies to be carried out considering these situations. In our study, we did not examine whether the decrease in RNFL thickness and the increase in corneal thickness observed due to isotretionin use improved after drug discontinuation or not.

In conclusion our study showed that oral isotretinoin therapy could cause regional thinning in RNFL and CCT. It is necessary to monitor the patients receiving systemic isotretinoin therapy closely for adverse effects in ocular system.

Ethics committee approval: Local Ethics Committee approval was obtained.

Informed consents: They were obtained.

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Conception and design, or analysis and interpretation of data: DU, LBS, AT

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Case report

mucosa

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Is vulvar purpura a component of plasma cell vulvitis or mucosal porosis?

Vulvar purpura plazma hücreli vulvit ya da mukozal porozun bir komponenti olabilir mi?

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Abstract

Here, we presented six women with isolated vulvar purpura. No associated lesions such as sclerosis, atrophy, or hypopigmentation were observed. All patients were in postmenopausal period. In this case series, we discussed if a non-blanching purpura could be a component of plasma cell vulvitis or "mucosal porosis". The possibility of vulvar purpura was questioned as a mucosal equivalent of dermatoporosis which is an age-related degenerative process in the skin. While senile purpura is one of the morphological findings of dermatoporosis, vulvar purpura might be a part of "mucosal porosis". Rapid response to topical estrogen was remarkable in all patients.

Key words: *dermatoporosis, mucosa, plasma cell vulvitis, porosis, purpura, vulva*

Öz

Bu yazıda, izole vulvar purpurası olan altı hastayı sunduk. Hiçbir hastada eşlik eden skleroz, atrofi ya da hipopigmentasyon gibi bulgular gözlenmedi. Hastaların tümü postmenopozal dönemde idi. Bu vaka serisinde, vulvada görülen purpurik lezyonların plazma hücreli vulvitin bir komponenti ya da yeni bir antite "mukozal poroz" olma olasılığını tartıştık. Vulvada görülen purpuranın, yaşlanmaya bağlı olarak deride tanımlanan dermatoporozun "mukozal" eşdeğeri olabileceği fikri ilginç olabilir. Senil purpura, dermatoporozun morfolojik bir bulgusu ise, belki de vulvar purpura mukozal porozun bir göstergesidir. Tüm hastalarda topikal östrojenle hızlı bir düzelme gözlenmesi bu teoriyi destekler niteliktedir.

Anahtar kelimeler*: dermatoporoz, menopoz, mukoza, plazma hücreli vulvit, poroz, purpura, deri, vulva*

Introduction

Although vulvar purpura is mostly observed as a component of lichen sclerosus (LS), it has been also associated with plasma cell vulvitis (Zoon's vulvitis) (PCV),[1,2] PCV-lichen aureus overlap,[3] and chronic intrapelvic conges-

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tion with increased venous pressure possibly due to abdominal ptosis.[4]

Dermatoporosis is an umbrella term to define degenerative changes in the aged skin such as senile purpura, stellate pseudoscars, skin atrophy and laceration, and dissecting hematomas as well. Different mechanisms might have a role in the development of dermatoporosis.[5] Here, we presented six cases with isolated vulvar purpura and discussed the possibility of "vulvar mucosal porosis". However, it is crucial to consider if those cases were plasma cell vulvitis (PCV) which is a well-known entity with proposed criteria by Virgili et al.[1]

Case reports

Some characteristics of patients were summarized in Table 1. The patients were examined by both a dermatologist and a gynaecologist in the Vulvar Clinic. They were referred from Gynaecology Clinic. All patients had similar dermatologic findings characterized by non-blanching yellow-red, macular purpuric lesions in the introitus and/or the inner labia minora (Figs. 1a, 2a and 3) (Table 1). Oral mucosa and skin examinations were normal. HIV serology was negative in all patients. Case 3 denied biopsy, cases 4, 5 and 6 denied both photography and biopsy. They all were treated with topical estriol cream once a day for 2 weeks, then twice a week for 3 months.

Informed consents were obtained in all six patients.

Case 1

A 57-year-old female was seen with the complaint of progressive vulvar discoloration (Fig. 1a), dyspareunia, and mild pruritus for one year. Fasting glucose and HbA1c were 138 mg/dl (N: 74-106 mg/dl) and 6.6% (N: 4-6%), respectively. A punch biopsy was taken from the purpuric area. Histopathology showed focal atrophy at the epithelium, dense plasma cell infiltration, erythrocyte extravasation and congestion in the lamina propria. In addition, the Lozenge shape keratinocytes were obtained at the epithelium. There was a dense plasma cell infiltration which consists of more than 50% of the cells in the lamina propria with CD-38 immunohistochemical staining. These findings were obtained in the focal area (Figs. 1b and 1c). Le-

Table 1. Clinical and laboratory characteristics of the patients

	Menopause	Location	Associated symptoms/findings	Comorbidity	Laboratory*
Case 1 Age 57	8 years	Introitus	Dyspareunia Mild pruritus	DM	Glucose ↑ HbA1C ↑ Others: N
Case 2 Age 50	5 months	Introitus	Pruritus	DM	N
Case 3 Age 48	1 year	Introitus	Pruritus	DM	Insulin ↑ Others: N
Case 4 Age 54	5 years	Introitus Inner aspects of labia minora	Dyspareunia Fissuration	No	N
Case 5 Age 57	7 years	Introitus	No	DM HT	N
Case 6 Age 52	4 years	Introitus	No	HT Cholecystectomy	N

* Fasting glucose, HbA1C, complete blood count, sedimentation rate, hepatic and renal functions, coagulation tests, Hepatitis B, C and HIV serologies; DM, Diabetes mellitus; HT, Hypertension

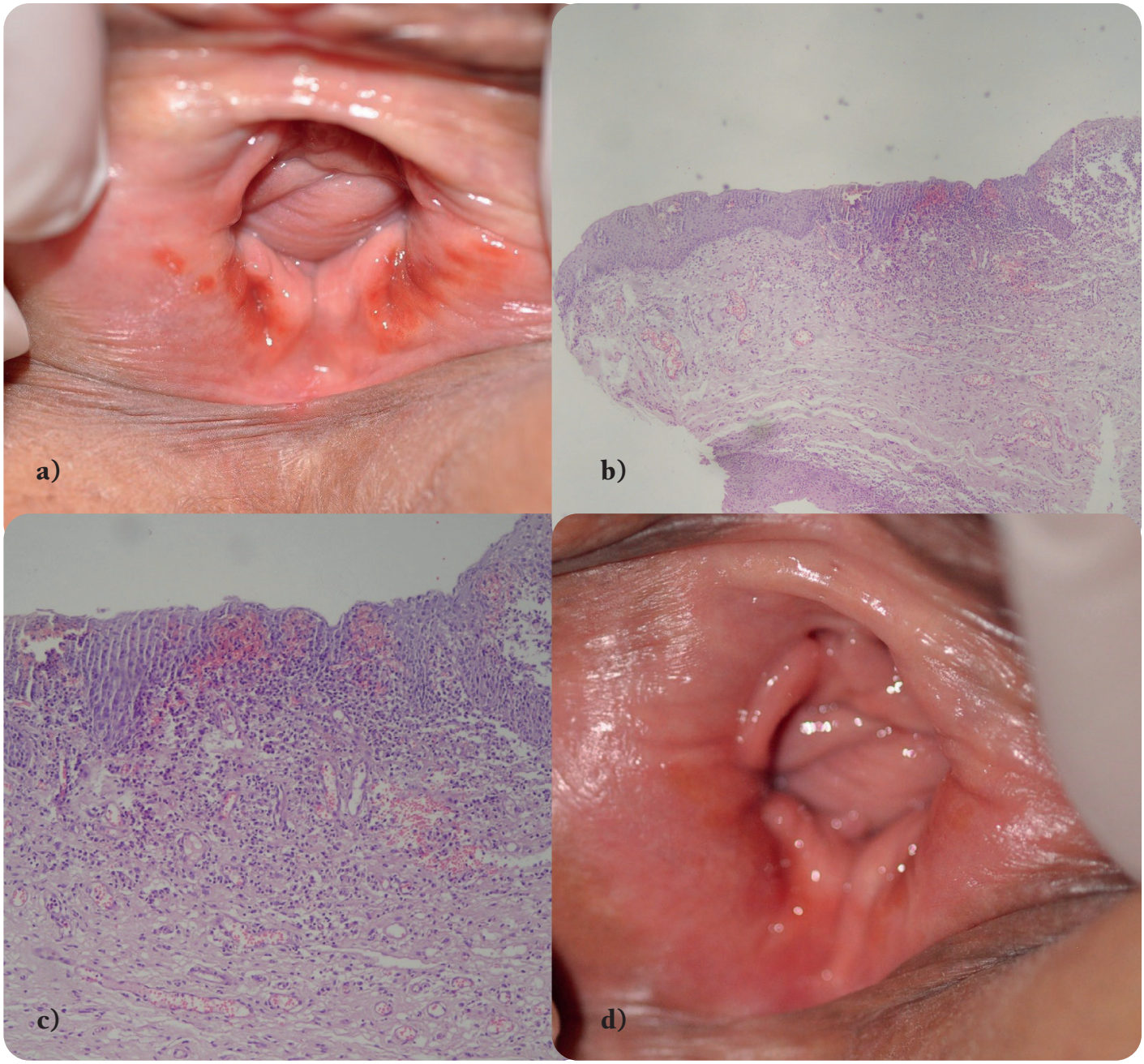

Fig. 1a. Vulvar purpuric discoloration, **1b.** Focal atrophy at the epithelium, dense plasma cell infiltration, erythrocyte extravasation and congestion in the lamina propria. (H.E.x4) **1c.** A dense plasma cell infiltration which consists of more than 50% of the cells in the lamina propria with CD-38 immunohistochemical staining. (H.E.x40) **1d.** Subsided lesions two weeks later with topical estrogen cream

sions subsided in the 2nd week of follow-up with estrogen cream (Fig. 1d).

Case 2

A 50-year-old female was referred for genital pruritus. Dermatologic examination was also consistent with lichen simplex chronicus in the supraclitoral area. Her past medical history was remarkable for diabetes mellitus. Histopathology of a punch biopsy showed similar findings except more atrophy in the epithelium than Case 1 (Fig. 2b). CD-38 staining showed plasma cells consisted of nearly 40% of whole infiltration (Fig.

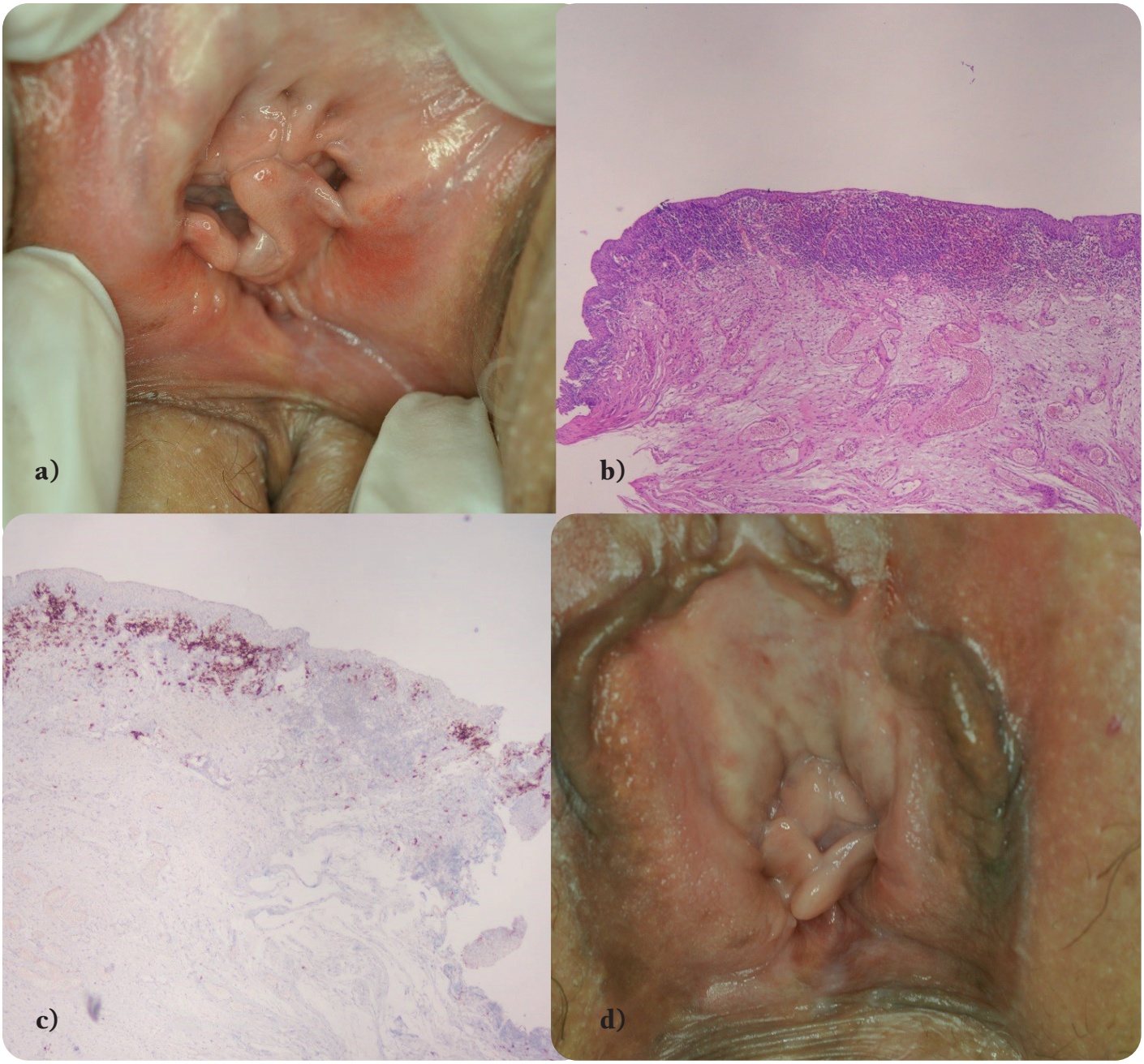

Fig. 2a. Vulvar purpuric discoloration **2b.** More atrophic epithelium and similar findings with case 1. (H.E.x4) **2c.** CD-38 staining showed plasma cells consisted of nearly 40% of whole infiltration (H.E.x40) **2d.** Almost clear examination two weeks later with topical estrogen

2c). The patient was lesion free in the 2nd week of follow-up with topical estrogen (Fig. 2d).

Case 3

A 48-year-old female was referred for genital pruritus. Dermatologic examination was also consistent with lichen simplex chronicus in the labium majus. Her past medical history was remarkable for diabetes mellitus. The patient had no lesion in the 3rd week of follow-up with topical estrogen.

Case 4

A 54-year-old female presented with dyspareunia and burning of the vulva started one year ago. A fissure

was also noticed in the lower part of the vulva in addition to purpuric lesions mentioned above. The lesions were disappeared after one month of treatment with estrogen cream.

Case 5

A 57-year-old female was referred for asymptomatic vulvar lesions. The patient was lesion-free after being treated with estrogen cream for two months.

Case 6

A 52-year-old female was referred for asymptomatic, purplish lesions in the vulva. The patient was lesion-free in 2nd month of applying estrogen cream.

Discussion

"Dermatoporosis" is a similar entity as osteoporosis defining a chronic fragility syndrome in the aging skin.[5] It is seen in elderly usually after the age of 60. Potential underlying mechanisms of fragile skin in dermatoporosis might be related to loss of extracellular matrix (ECM), alterations in skin viscoelasticity, ultraviolet light (UVL)-mediated effects, and hyaluronate-and CD44-dependent growth factor signalization defects.[5] Senile purpura is one of the morphological markers of dermatoporosis and results from spontaneously or repetitive minimal trauma causing dermal haemorrhage in the absence of coagulation defects.[5] Although mucosal equivalent of dermatoporosis has not been previously reported, it is likely that all the mentioned mechanisms except for the effect of UVL may cause vulvar degenerative process. Estrogen deficiency due to menopause might have an additional contributing factor for vulva. Therefore, "vulvar mucosal porosis" is a reasonable term to define vulvar degenerative changes such as purpura seen in our patients. Vulvar purpura might be a mucosal type of senile purpura classified as a morphological type of dermatoporosis. Frictional trauma together with postmenopausal atrophy and vulvar xerosis may induce purpura. The presence of introitus involvement (all cases) and dyspareunia (two cases) suggest that coitus might be a contributing trauma as well.

Presented cases were between the ages of 48 and 57 years (Table 1). Considering dermatoporosis starts after the age of 60 years,[5] it is reasonable to hypothesize that mucosal fragility may develop earlier than skin. Furthermore, decreased physical activity and sexual intercourse in elderly may decrease frictional trauma and subsequent purpura.

Vulvar purpura is mostly observed as a component of LS. Unlike LS, none of our patients had sclerosis, atrophy, and hypopigmentation. Of interest, our patients only presented with nonpalpable purpura contrary to Henoch-Schönlein vasculitis. All patients denied prior usage of systemic or topical steroid, which could also cause cutaneous purpura. Interestingly, lichen aureus associated with PCV was reported as a rare cause of localized purpura in the vulva.[3] Authors emphasized trauma might have a possible role of both entities.[3] In consideration to the similarities with PCV, it is questionable if mucosal porosis is a real entity (Table 2). PCV is a rare but well-known entity of ISSVD (International Society for The Study of Vulvovaginal Disease) classification, whereas mucosal porosis is a hypothesis we suggest as a result of a degenerative process. We presented six cases totally with three cases had a clinical picture and only two had histopathological examination. Clinical similarities and rapid efficacy of topical estrogen in all six patients might support and raise a question the possibility of a new entity (Table 2). Histopathological findings in our patients should be interpreted scrupulously. Although Virgili et al.[1,2] defined histopathologic criteria in PCV and emphasized plasma cell infiltration should be more than 25%, plasma cell infiltration could be less than usual as in some cases of plasma cell balanitis.[6] We found dense lichenoid subepithelial infiltrate composed largely (more than 50% in the first case, 40% in the second case) of plasma cells. Our findings obtained in the epithelium and the lamina propria at the focal area. Virgili et al.[1] also proposed erythrocyte extravasation is not a specific finding of PCV, since micro trauma or biopsy may induce it. Instead, they emphasized the importance of hemosiderin deposition which we did not observe.[1] Focal concurrence of both epithelial atrophy and

Table 2. Detailed comparison of the features of plasma cell vulvitis and our patients

	Plasma cell vulvitis (PCV)	Presented cases
Age of diagnosis	54.9 (49-74)	53 (48-57)
Symptoms	Asymptomatic (16.7%)[2] Pruritus (44.4%)[2] Dyspareunia (52.8%)[2] Burning (80.6%)[2]	Asymptomatic (2 cases) Pruritus (3 cases) Dyspareunia (2 cases)
Clinical features	Solitary sharply defined red-brown glistening patch, 1-3 cm Occasionally multiple, pinpoint purpuric spots and erosive lesions	Bilateral, macular non-blanching purpuric, yellow-red patches
Locations	Mainly inner surface of labia minora and periurethral area. Introitus can be involved	Introitus (6 cases) Inner surface of the labia minora (2 cases)
Histopathology		
Epithelial atrophy	Yes (13/18)[1]	Focal in inflammatory area, acanthosis in noninflammatory area (Case 1,2)
% plasma cell infiltration	Yes ≥50%: 11/18[1] 25-50: 5/18[1] <25%: 2/18[1]	Focal >50% (Case 1) ~%40 (Case 2)
Lozenge-shaped keratinocytes	2/18[1]	1/2
Slight spongiosis	Yes[1]	No (Case 1,2)
Vascular dilation	Yes[1]	Yes (Case 1,2)
Erythrocyte extravasation	Nonspecific[1]	Yes (case 1,2)
Hemosiderin deposition	Yes (15/18)[1]	No (Case 1,2)
Treatment	Lack of evidence for estrogen efficacy Estrogen as a treatment only in one study (improvement in only 16% of 36 patients)	Rapid improvement with topical estrogen in all patients

inflammation has not been mentioned in PCV. All of these histopathological findings seen in Case 1 and 2 could be a feature of a degenerative process (Table 2).

We observed a rapid improvement with topical estrogen in all patients. PCV has a chronic course and no effective treatment regimens have been established.[2] Topical steroids and calcineurin inhibitors are effective improving PCV symptoms rather than clinical signs.[7] There is no evidence estrogen is effective in PCV, although Virgili et al.[2] found estrogen is effective in only 16% of 36 PCV patients. Li et al.[3] reported topical estrogen increased the lesions in their PCV and lichen aureus overlap case, and they suggested this could be due to delayed type hypersensitivity reaction. Topical and systemic estrogens have not been mentioned for the treatment of dermatoporosis since there is no data about estrogen deficiency in dermatoporosis. However, estrogen might be the only reasonable agent

in estrogen-sensitive areas such as vulva in mucosal porosis.

Genitourinary syndrome of menopause (GSM) is a relatively new term describing signs and symptoms of genital, sexual and lower urinary tract of menopause. Tissue fragility, fissures and petechia have been reported among the signs of GSM.[8] Unlike our observation in patients, those symptoms are progressive and do not to resolve spontaneously.[9] Although changes of vaginal mucosa were well-described, vulvar histopathological findings were not mentioned. Nevertheless, vulvar porosis may basically define the similar entity of this spectrum with histopathological findings.

In conclusion, vulvar purpura in postmenopausal women may result from different mechanisms. Firstly, clinicians should exclude LS as an important cause of vulvar purpura. PCV is another cause. In case of an isolated vulvar purpura, decreased estrogen levels leading to vulvovaginal atrophy and xerosis may have a contributing role as in dermatoporosis. We are aware of the tendency of ISSVD to simplify and clarify the diagnostic categories of vulvar conditions. Suggestion of a new diagnostic category will need to be extremely well defined, including multiple histopathologic and gross examples, and describe a clear pathophysiologic mechanism to be considered as a novel category. However, these cases did not show an exact match for PCV or another entity. Mucosal porosis might be resulted in the presence of estrogen deficiency and contributing comorbidities such as diabetes mellitus (four cases) (Table 1). Further reports particularly ultra structural ones as in the study of Kaya et al.[5] in dermatoporosis might reveal if mucosal porosis is a novel entity or associated or a triggering factor of PCV. Vulvar purpura or "vulvar mucosal porosis" may be a common but neglected entity due to its minor symptoms or asymptomatic character mostly.

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Informed consent: The author certifies that she has obtained all appropriate consent forms from the patient.

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Authorship contributions:

Conception and design, or analysis and interpretation of data: AK, DS

Drafting the manuscript or revising the content: AK, DS, MY

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Case report

mucosa

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Severe bullous pemphigoid after Vaxzevria COVID-19 vaccination

Vaxzevria COVID-19 aşısı sonrasında gelişen şiddetli büllöz pemfigoid

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Abstract

Bullous pemphigoid has been described in a small number of cases secondary to the Pfizer and Moderna COVID-19 vaccinations. This is the first reported case of bullous pemphigoid triggered by the Oxford-AstraZeneca Vaxzevria COVID-19 vaccination. His first symptoms occurred four weeks after his first dose, and were confirmed on direct immunofluorescence and with positive BP180 antibodies.

Key words: *Bullous pemphigoid, covid-19, vaccination, autoimmune blistering disease*

Öz

Pfizer ve Moderna COVID-19 aşılarına sekonder büllöz pemfigoid az sayıda olguda tanımlanmıştır. Bu, Oxford-AstraZeneca Vaxzevria COVID-19 aşısı tarafından tetiklenen bildirilmiş ilk büllöz pemfigoid vakasıdır. Olgunun ilk semptomları, aşının ilk dozundan dört hafta sonra ortaya çıkmış ve büllöz pemfigoid tanısı direkt immünofloresan test ve BP180 antikor pozitifliği ile doğrulanmıştır.

Anahtar kelimeler: *Büllöz pemfigoid, covid-19, aşı, otoimmün büllöz hastalık*

Case

A 71-year old Chinese male developed pruritic urticarial lesions over his arms four weeks after his first dose of the Vaxzevria Oxford-AstraZeneca COVID-19 vaccination. Over the next six weeks he developed extensive bullae over the lateral edges of his feet that then spread over his entire body (Fig. 1). At the onset of blisters, he had a biopsy revealing subepidermal blistering; direct immunofluorescence (DIF) test revealed continuous, linear deposition of complement (C3) and IgG at the dermo-epidermal junction (Fig. 2). On enzyme-linked immunosorbent assay (ELISA), he had positive BP180 antibodies at a titre >5.00 and negative BP230 antibodies.

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His medical history was significant for type 2 diabetes mellitus, an achilles tendon rupture and benign prostatic hypertrophy managed with metformin, saxagliptin and tamsulosin. These medications had been unchanged for approximately five years. Since bullous pemphigoid may be triggered by gliptins, but our patient had been on saxagliptin for over five years, it is possible that he may have had autoantibodies to BP180 without a rash and symptoms but these were then triggered by the augmentation of his skin inflammation related to the Covid-19 vaccine. As such, his gliptin was ceased. He had no known drug allergies, is a non-smoker and non-drinker of alcohol. He had not commenced on any new medications or had any recent illnesses and there was no cognitive impairment or neurological dysfunction.

At diagnosis, his Bullous Pemphigoid Disease Area Index (BPDAI)[1] confirmed severe bullous pemphigoid with an activity score of 91 and damage of 10. He had extensive blistering and erosions affecting his entire body. There was one erosive lesion affecting his mouth, but no involvement of his ocular or anogenital mucosa. He was commenced on 0.5 mg/kg of oral prednisolone,

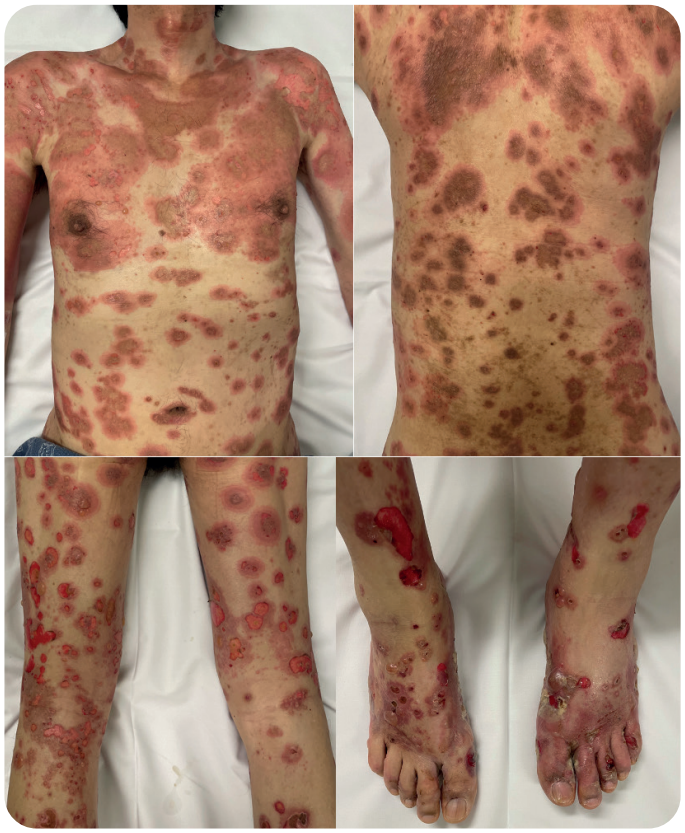

Fig. 1. Clinical photos of baseline with extensive blistering and erosions

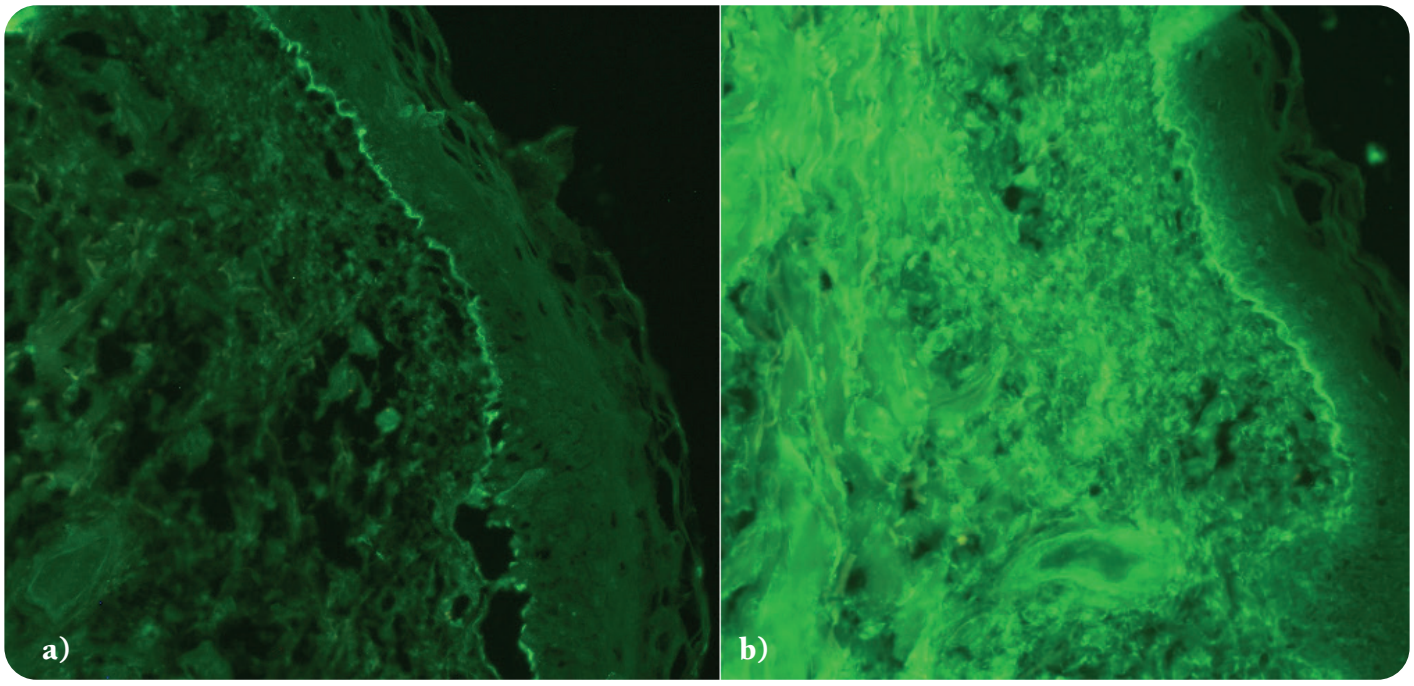

Fig. 2. Direct Immunofluorescence test with continuous, linear deposition of C3(a) and IgG(b) at the dermo-epidermal junction

topical mometasone furoate 0.1% to his body twice daily with emollients, doxycycline 100 mg bid po and nicotinamide 500 mg tid po. After two weeks of treatment, his BPDAI had reduced to an activity score of 65 and damage score of 10 with extensive post-inflammatory hyperpigmentation but minimal new blisters.

Bullous pemphigoid has been reported in 10 previous cases after COVID-19 vaccinations.[2,3] Tomayko et al.[2] report 8 cases of confirmed bullous pemphigoid on direct immuofluorescence or BP180/230 ELISA. Five of these cases had a positive BP180 in addition to positive direct immunofluorescence. All of these cases were after either Pfizer or Moderna vaccinations. Of these cases, two occured five days after the first Pfizer vaccination and six occurred 3-21 days after the second dose of either Pfizer or Moderna vaccinations. Larson et al.[3] report two further cases of bullous pemphigoid confirmed on direct immunofluorescence test alone. One of these developed three weeks after the first dose of the Pfizer vaccination and the other developed two weeks after the second dose of Moderna.

This is the first description of bullous pemphigoid triggered from the Vaxzevria Oxford-AstraZeneca COVID-19 vaccine.

Informed consent: Consent was gained from this patient for publication and presentation of his clinical information, case and images.

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Letter to editor

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Chronic mucocutaneous candidiasis: a rare disease

Kronik mukokutanöz kandidiyazis: nadir bir hastalık

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Dear editor,

An 11-year-old female patient was admitted to our clinic with complaints of whiteness in the mouth and crusty lesions on the nose. It was learned that the patient's complaints started two years ago, recurred every 3-4 months, and partially regressed with antifungal treatments. Dermatological examination revealed hypopigmented patches with irregular borders on the face, consistent with vitiligo, and plaques with yellowish crusts on the nose. White plaques consistent with candida infection were seen on the tongue. Yellowish discoloration and hyperkeratosis were observed on the 5th nail of the left hand (Fig. 1). Microscopic examination of the whitish tongue and scrapings of the hyperkeratotic lesion of the nail revealed fungal hyphae and pseudospores. *C Albicans* was positive in fungal culture made from samples taken from tongue and nail.

Based on the current findings, the patient was diagnosed with chronic mucocutaneous candidiasis (CMC). Complete blood count, liver function tests, blood glucose, calcium, phosphate and magnesium levels, Human Immunodeficiency virus (HIV) test, thyroid function tests, parathyroid stimulating hormone, follicle stimulating hormone, luteinizing hormone, prolactin, testosterone, corticotropin test and serum cortisol values were within normal ranges. Systemic fluconazole treatment was started for the patient, but since a fixed drug eruption developed 1-day after the drug use, systemic itraconazole treatment was started. At the follow-up, it was observed that the lesions on the oral mucosa were completely resolved, and the lesion on the nail was partially resolved after four weeks. CMC is a rare disease characterized by chronic and refractory infections of the skin, mucous membranes or nails caused by fungi of the genus Candida.[1] Some immunological and hormonal abnormalities have been associated with CMC. Factors that predispose the host to CMC infection may be autosomal or acquired.[1-3] Genetic mutations, such as mutations in the signal transducer and activator of transcription 1 are known to cause immune system dysfunctions in some forms of CMC. In addition, an imbalance between T helper

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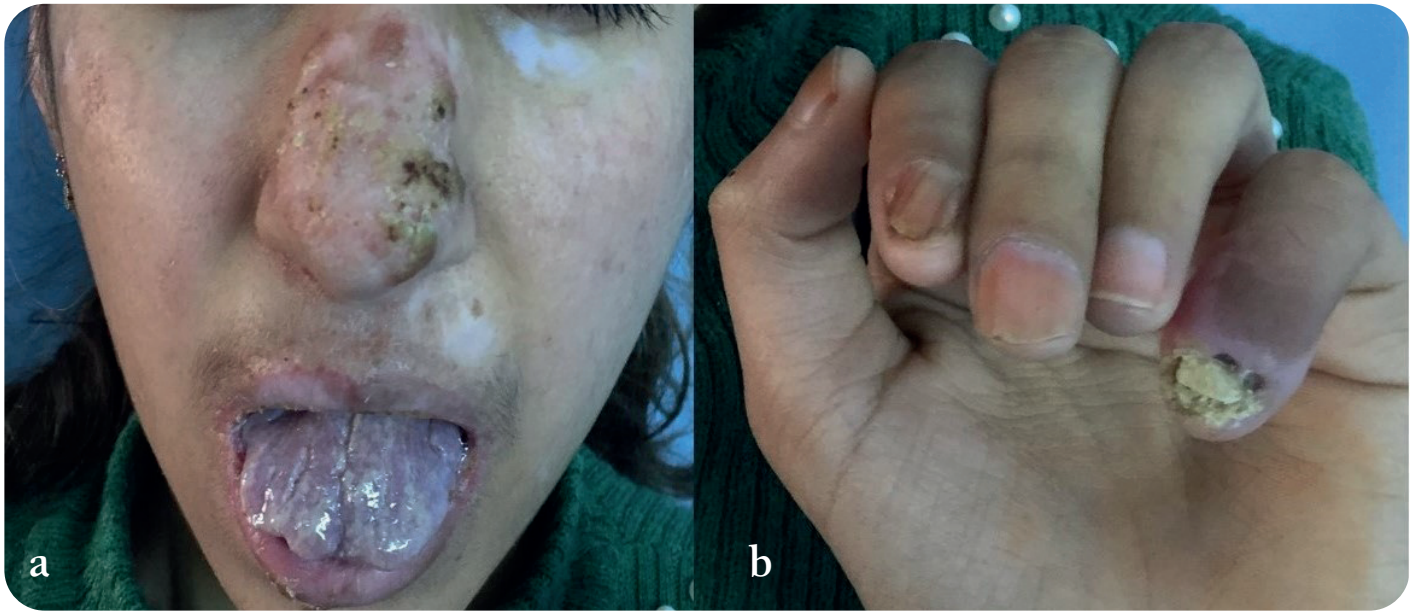

Fig. 1a. Hypopigmented patch with irregular borders on the face and plaques with yellowish crusts on the nose. Whiteness on the tongue consistent with candidiasis in the oral mucosa, **1b.** Yellowish discoloration and hyperkeratosis on the 5th nail of the left hand

1 (Th1) and Th2 immune responses has been reported in patients with CMC.[3,4-6] No genetic analysis was performed in our patient. Immunoglobulin levels were found to be within normal range in our patient.

CMC is seen with equal frequency in men and women and usually occurs in infancy or early childhood.[2] In patients with CMC, chronic or recurrent candidal infections are seen especially in the nails, skin, mouth and genital mucosa due to *C. albicans*.[2,4,7] Various disorders such as vitiligo, alopecia, bone marrow abnormalities, myasthenia gravis, thymoma, endocrine dysfunctions and malabsorption syndromes may occur in patients with CMC.[2,4,8-10] Our patient also had vitiligo. In our patient, vitiligo started 1 year after the diagnosis of mucocutaneous candidiasis.

The diagnosis of CMC is made on the basis of physical examination findings, potassium hydroxide (KOH) preparation results, fungal culture, and history of recurrent and resistant candidiasis.[2,10] To detect endocrine dysfunctions and other diseases associated with CMC, complete blood count, liver function tests, blood glucose or glycosylated hemoglobin test, serum electrolyte levels, HIV test, thyroid function tests, follicle stimulating hormone, luteinizing hormone, parathyroid stimulating hormone, prolactin, testosterone, corticotropin test and serum cortisol levels should be measured.[1,2,4,7-10] No accompanying endocrinopathy was detected in our patient.

Topical treatments are generally not effective in the treatment of CMC. Systemic fluconazole, itraconazole and posaconazole are mostly first-line treatment options. Voriconazole and liposomal amphotericin B are used as second-line therapies. Treatment of CMC can be difficult and recurrence is common following discontinuation of therapy.[9-10] We treated our patient with itraconazole because fix drug eruption developed due to fluconazole use.

In conclusion, it should be kept in mind that CMC, which is a rare disease, may be seen together with skin diseases such as vitiligo and should be followed closely in terms of accompanying endocrinopathies.

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