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RESEARCH ARTICLE

Does Removal Of Volar Locking Plate Affect Patient Functional Outcomes?

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Abstract

Introductıon: The aim of our study is to evaluate the effect of volar locking plate (VLP) removal on functional scores.

Methods: In this retrospective study, between January 2019 and January 2024, medical records of our institution were reviewed and patients who underwent VLP removal were included in the study. Demographic characteristics of the patients, follow-up time until VLP removal and reasons of VLP removal were evaluated from medical records. Preoperative and postoperative 3rd month Disabilities of Arm, Shoulder and Hand (DASH) scores were evaluated. Soong classification was performed on lateral wrist radiographs.

Results: Thirty-eight patients (24 male, 14 female) patients were included in the study. The mean age of all patients was 51.23±15.6 years. The mean time from VLP fixation to implant removal was 17.42±12.42 months. Patients who underwent implant removal were evaluated according to the Soong classification. 18 of the patients (%47.36) were grade 0, 16 of the patients (%42.1) were grade 1 and 4 of the patients (%10.54) were grade 2. The most common removal reason was patient request (n=26, %68.42). Preoperative mean DASH score was 19.1 and postoperative 3rd month mean DASH score was 8.2. There was a significant difference between preoperative and postoperative 3rd month DASH scores. ($p<0.001$) When patients were asked whether they would choose to implant removed again if they were in the same situation, %94.7 of the patients stated that they would choose implant removal again.compared to those with only one previous cesarean section ($p=0.015$).

Conclusion: VLP removal provided significant improvement in the patients' functional outcomes. The most common reason for VLP removal was patient request.

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Introduction

Distal radius fractures (DRF) are one of the most common fracture in adults.[1] The incidence of DRF in the adult population is higher in women. However, the incidence of DRF in adolescents is higher in males.[2,3] The most common cause of trauma in the elderly population is falling from standing height and osteoporosis is the most important risk factor.[4] And the prevalence of DRF will continue to rise as the elderly population increases.[5,6]

Although the trend in the treatment of DRF is towards surgery, the most frequently applied treatment methods are non-operative methods.[7,8] With the development of volar locking plates (VLP), the number of surgically treated DRFs has increased. 16% of all fractures requiring orthopedic surgical treatment are DRF.[9] The advantages of VLP are more stable fixation, shorter immobilization period and fewer complications.[10,11] However, tendon irritation, nerve irritation or infection may develop after VLP fixation.[12-14]

If there are no complications, most surgeons do not require VPL removal.[15,16] A wide range of VLP removal rates have been reported in different studies.[17,18] Although satisfactory results have been reported in the surgical treatment of DRF with VLP, VLP removal is required in some cases.[19-21] Main reasons of VLP removal are pain, tendon rupture, malunion, infection, nonunion, tenosynovitis and tendon rupture.[22] Reasons for VLP removal include patient request and surgeon discretion, in addition to complications.[23] Soong et al developed a classification system to determine the risk of tendon rupture after VLP treatment.[24] In our study, we aimed to evaluate the effect of VLP removal on functional scores.

Material and Methods

Approval for the study was granted by the institutional review board of the authors' affiliated institutions (Project number: TABED 1-24-186, date: 08.05.2024). All the researchers who participated in the study signed the most recent version of the Helsinki Declaration. All patients signed an informed consent form.

In this retrospective study, between January 2019 and January 2024, medical records of our institution were reviewed and patients who underwent VLP removal were included in the study. Patients over 18 years were included in the study. Patients requiring additional fixation material, patients treated with any material other than VLP, patients with bilateral DRF, neurovascular injury, multiple trauma, pathological fracture, previous DRF and patients with insufficient medical records were excluded from the study. Demographic characteristics of the patients, follow-up time until VLP removal and reasons of VLP removal were evaluated from medical records.

All VLP removals were performed under anesthesia. (general anesthesia or nerve block) And modified henry approach was used. (Figure 1) Tourniquet was used for all surgeries. After VLP removal, range of motion (ROM) exercises were allowed immediately. Preoperative and postoperative 3rd month Disabilities of Arm, Shoulder and Hand (DASH) scores were evaluated.

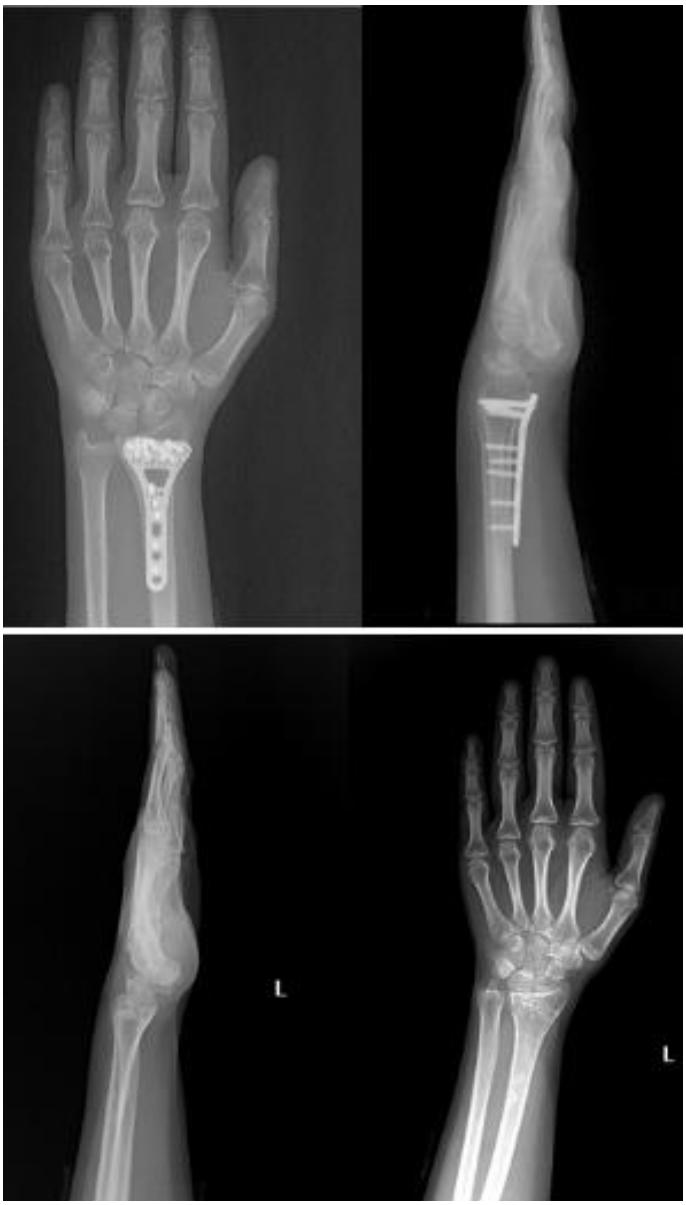

Figure 1: Preoperative and postoperative radiography of volar locking plate removal

The PACS system was used for radiological evaluations. And Soong classification was performed on lateral wrist radiographs. Soong et al developed a classification system based on the prominence of the volar plate. In the Soong classification, a line is drawn parallel to the volar cortex, starting from the volar rim of the radius. If the volar plate is proximal to the line, it is called grade 0. If the volar plate is at the same level as the line, it is called grade 1. And if the volar plate is distal to the line, it is called grade 2. (Figure 2)

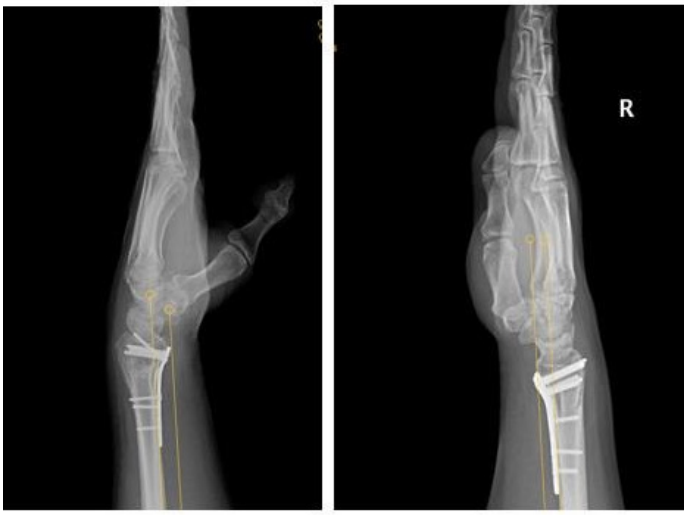

Figure 2: Soong classification

Statistical analysis:

Statistical data analyses were performed using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using the chi-square test. The suitability of continuous variables to normal distribution was examined by calculating skewness and kurtosis values. Continuous variables with normal distribution were compared using the independent samples t test, and continuous variables with non-normal distribution were compared using the Mann-Whitney U test. Measurements taken before and after the surgery were analyzed using the dependent sample t test. The results were evaluated within 95% confidence intervals, and $P < 0.05$ was considered significant.

Results

Between January 2019 and January 2024, 44 volar plate removal were performed. Six patients did not meet the inclusion criteria and they were excluded from the study. Thirty-eight patients (24 male, 14 female) patients were included in the study. The mean age of all patients was 51.23±15.6 years. The mean age of female patients was 50.64±15.75 years and the mean age for male was 51.58±14.83 years. Eighteen of the patients (10 male, 8 female) dominant side was operated. The mean time from VLP fixation to implant removal was 17.42±12.42 months. Implant removal of 29 patients was performed within the first 2 years. (Table 1)

Table 1: Characteristics of Patients

	Female (n=14)	Male (n=24)	All patients (n=38)
Age	44.92±15.6	51.58±14.83	51.23±15.6
Side	8 left, 6 right	12 left, 12 right	20 left, 18 right
Dominant side	8	10	18
Mean time from VLP fixation to implant removal	16.49±11.89	17.96±13.27	17.42±12.42
Implant removal in first 2 years	14	15	29

Patients who underwent implant removal were evaluated according to the Soong classification. 18 of the patients (%47.36) were grade 0, 16 of the patients (%42.1) were grade 1 and 4 of the patients (%10.54) were grade 2.

The reasons of implant removal were evaluated. And the most common reason was patient request (n=26, %68.42). The other reasons were carpal tunnel syndrome (n=2, %5.26), screw joint penetration (n=1, %2,64), pain (n=4, %10.53), foreign body sensation (n=1, %2,63), stiffness (n=2, %5.26) and cold intolerance (n=2, %5.26). Median nerve decompression was performed for the patients with carpal tunnel syndrome in the same session.

Clinical outcomes were evaluated with DASH score. Preoperative mean DASH score was 19.1 and postoperative 3rd month mean DASH score was 8.2. There was a significant difference between preoperative and postoperative 3rd month DASH scores. ($p<0.001$)

After implant removal only 2 minor complications were reported. One patient had superficial infection and one patient had numbness on the incision. Superficial infection was treated with oral antibiotics. And numbness on the incision resolved within 6 months.

When patients were asked whether they would choose to implant removed again if they were in the same situation, %94.7 of the patients stated that they would choose implant removal again.

Discussion

In the current study, we determined that VLP removal provided significant improvement in the patients' functional outcomes. The most common reason for VLP removal was patient request, and almost 90% of the patients who underwent implant removal were grade 0 or 1 according to the Soong classification.

There are studies in the literature indicating different implant removal rates between 0% and 100% after distal radius fracture fixation.[17] While some surgeons perform routine implant removal, some surgeons perform implant removal due to patient request or complications. Palola et al. determined that plate removal rates were over 20% between 1998 and 2004, but it decreased to less than 13% after 2008.[25] The reason of the implant removal rate decrease was attributed to improvements in plate design and increase in surgical experience. Yamamato et al. reported that increase of the rate of implant removal is associated with the increase of the complication rate.[17] In our study, we performed implant removal due to patient request and complications. In previous studies, the most common reason for implant removal was pain.[27] In the current study, patient request was the most common reason for implant removal and the second most common reason was pain.

There are different reasons for VLP removal like infection, tendon irritation, tendon rupture, neurovascular injury, nerve irritation, non-union and malunion. However, some patients want implant removal without any clinical symptoms. Removals performed without symptoms are called routine removals.[17] In many studies, the most common reason for removal is routine removal. Lee et al. reported that in their study routine removals accounted for %73.8 of all removals.[29] In our study, routine removal was %68.42.

Flexor tendon irritation may develop due to distally plate placement, especially in joint-related and comminuted fractures. A higher rate of implant removal is expected in patients with more distal VLP placement. However, no difference was reported in the implant removal rates of joint-related and comminuted fractures.[17] Therefore, we did not evaluate the fracture types separately in our study.

According to the Soong classification, most cases with grade 2 result in implant removal.[26] Selles et al. reported that patients with grade 2 Soong classification underwent 6 times more implant removal than patients with grade 0.[26] In our study, we evaluated only patients who underwent VLP removal. Therefore, we could not give implant removal rates according to Soong classification. However, in line with the literature, the majority of patients who underwent implant removal were grade 0 or 1 according to Soong classification.[29]

Different studies have reported improvement in functional outcomes with implant removal after distal radius fracture fixation.[22] Lee et al. determined significant improvement between preoperative and postoperative DASH scores.[29] In the current study, DASH score improved from 19.1 to 8.2. A significant improvement in functional results was observed in patients who underwent routine removal, as well as in symptomatic patients. The increase in functional score with routine removal raises the question of whether implant removal should be performed in all suitable patients. However, this question can be answered with larger studies.

Various complications may develop with implant removal like infection, refracture, nerve injury and tendon injury. Additionally, locking plate designs may cause difficulties in implant removal.[30] We encountered 2 minor complications in our study. One patient had superficial infection and one patient had numbness on the incision. Superficial infection was treated with oral antibiotics. And numbness on the incision resolved within 6 months.

Our study have some limitations. Firstly, different types of VLP removed. But they were not evaluated separately. Secondly, only functional outcomes of the patients who underwent implant removal were evaluated. We did not have implant retention group. Thirdly, the fracture patterns of the patients included in the study were not evaluated separately. Different fracture types may affect functional outcomes. More valuable data can be obtained with larger patient groups.

Conclusion

VLP removal provided significant improvement in the patients' functional outcomes. The most common reason for VLP removal was patient request.

References

1. Court-Brown CM, Caesar B. Epidemiology of adult fractures:va review. Injury 2006;37(8):691–697.
2. Hagino H, Yamamoto K, Ohshiro H, Nose T. Increasing incidence of distal radius fractures in Japanese children and adolescents. J Orthop Sci 2000;5(4):356–360.
3. Flinkkila T, Sirnio K, Hippi M, Hartonen S, Ruuhela R, Ohtonen P, Hyvonen P, Leppilahti J. Epidemiology and seasonal variation of distal radius fractures in Oulu, Finland. Osteoporos Int 2011;22(8):2307–2312.
4. Hevonkorpi TP, Launonen AP, Huttunen TT, Kannus P, Niemi S, Mattila VM. Incidence of distal radius fracture surgery in Finns aged 50 years or more between 1998 and 2016 – too many patients are yet operated on? BMC Musculoskelet Disord 2018;19(1):70.
5. Baron JA, Karagas M, Barrett J, Kniffin W, Malenka D, Mayor M, Keller RB. Basic epidemiology of fractures of the upper and lower limb among Americans over 65 years of age. Epidemiology 1996;7(6):612–618.
6. Levin LS, Rozell JC, Pulos N. Distal Radius fractures in the elderly. J Am Acad Orthop Surg 2017;25(3):179–187.
7. Huetteman HE, Shauver MJ, Malay S, Chung TT, Chung KC. Variation in the treatment of distal radius fractures in the United States: 2010 to 2015. Plast Reconstr Surg 2019;143(1):159–167.
8. Mellstrand-Navarro C, Pettersson HJ, Tornqvist H, Ponzer S. The operative treatment of fractures of the distal radius is increasing: results from a nationwide Swedish study. Bone Jt J 2014;96-B(7):963–969.
9. Ruch DS, McQeen MM (2015) Distal radius and ulna fractures. In: Bucholz RW, Beaty JH, Rockwood CA, Jr; Green DP (eds) Rockwood and Green's fractures in adults, 2015;vol 1, 7th edn. Wolter Kluwer Health/Lippincott, Wiliams & Wilkins, Philadelphia.
10. Jeudy J, Steiger V, Boyer P, Cronier P, Bizot P, Massin P. Treatment of complex fractures of the distal radius: a prospective randomised comparison of external fixation 'versus' locked volar plating. Injury 2012;43(2):174–179.
11. McFadyen I, Field J, McCann P, Ward J, Nicol S, Curwen C. Should unstable extra-articular distal radial fractures be treated with fixed-angle volar-locked plates or percutaneous Kirschner wires? A prospective randomised controlled trial. Injury 2011;42(2):162–166.
12. Gyuricza C, Carlson MG, Weiland AJ, Wolfe SW, Hotchkiss RN, Daluiski A. Removal of locked volar plates after distal radius fractures. J Hand Surg Am 2011;36(6):982–985.
13. Alter TH, Sandrowski K, Gallant G, Kwok M, Ilyas AM. Complications of volar plating of distal radius fractures: a systematic review. J Wrist Surg 2019;8(3):255–262.
14. Musgrave DS, Idler RS. Volar fixation of dorsally displaced distal radius fractures using the 2.4-mm locking compression plates. J Hand Surg Am 2005;30(4):743–749.
15. Dennison DG. Distal radius fractures and titanium volar plates: should we take the plates out? J Hand Surg Am 2010;35(1):141–143.
16. Busam ML, Esther RJ, Obremskey WT. Hardware removal: indications and expectations. J Am Acad Orthop Surg 2006;14(2):113–120.
17. Yamamoto M, Fujihara Y, Fujihara N, Hirata H. A systematic review of volar locking plate removal after distal radius fracture. Injury 2017;48(12):2650–2656.
18. Arora R, Lutz M, Hennerbichler A, Krappinger D, Espen D, Gabl M. Complications following internal fixation of unstable distal radius fracture with a palmar locking-plate. J Orthop Trauma 2007;21(5):316–322.
19. Berglund LM, Messer TM. Complications of volar plate fixation for managing distal radius fractures. J Am Acad Orthop Surg 2009;17(6):369–377
20. Gyuricza C, Carlson MG, Weiland AJ, Wolfe SW, Hotchkiss RN, Daluiski A. Removal of locked volar plates after distal radius fractures. J Hand Surg Am 2011;36(6):982–985.
21. Satake H, Hanaka N, Honma R, Watanabe T, Inoue S. Complications of distal radius fractures treated by volar locking plate fixation. Orthopedics 2016;39(5):e893–e896.
22. Snoddy MC, An TJ, Hooe BS, Kay HF, Lee DH, Pappas ND. Incidence and reasons for hardware removal following operative fixation of distal radius fractures. J Hand Surg Am 2015;40(3):505–507.
23. Tan A, Chong A. Reasons for implant removal after distal radius fractures. J Hand Surg Asian-Pacific 2016;21(3):321–325.
24. Soong M, Earp BE, Bishop G, Leung A, Blazar P. Volar locking plate implant prominence and flexor tendon rupture. J Bone Joint Surg Am. 2011;93(4):328e335.

25. Palola V, Ponkilainen V, Huttunen T, Launonen A, Mattila VM. Incidence for volar locking plate removal following distal radius fracture surgery. Arch Orthop Trauma Surg. 2021 Aug;141(8):1297-1302.
26. Selles CA, Reerds STH, Roukema G, van der Vlies KH, Cleffken BI, Schep NWL. Relationship between plate removal and Soong grading following surgery for fractured distal radius. J Hand Surg Eur Vol. 2018 Feb;43(2):137-141.
27. Lutsky KF, Beredjiklian PK, Hioe S, Bilello J, Kim N, Matzon JL. Incidence of hardware removal following volar plate fixation of distal radius fracture. J Hand Surg Am 2015;40(12):2410–2415.
28. Rubensson CC, Ydreborg K, Boren L, Karlander LE. Flexor tendon repair after rupture caused by volar plate fixation of the distal radius. J Plast Surg Hand Surg 2015;49(2):112–115.
29. Lee JK, Lee Y, Kim C, Kim M, Han SH. Volar locking plate removal after distal radius fracture: a 10-year retrospective study. Arch Orthop Trauma Surg. 2021 Oct;141(10):1711-1719.
30. Vos DI, Verhofstad MH. Indications for implant removal after fracture healing: a review of the literature. Eur J Trauma Emerg Surg 2013;39(4):327–337.

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RESEARCH ARTICLE

Scar Endometriosis After Cesarean Section; Our Clinical Experiences, 32 Cases of Cesarean Scar Endometriosis

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Abstract

Introductıon: Scar endometriosis is a type of rare endometriosis that develops following obstetric or gynecological surgeries. The aim of our study is to share our clinical experiences regarding scar endometriosis, which is becoming more common due to increasing cesarean operations, and to contribute to the literature on this subject.

Methods: A total of 32 patients who underwent surgery due to scar endometriosis participated in our study. The patients' demographic and clinical characteristics, size and location of the lesion determined by imaging methods and histopathological results were recorded and analyzed.

Results: The mean age of the patients was 34.81±6.52 years, with 46.9% having undergone one cesarean section and 53.1% having undergone two or more cesarean sections. Scar endometriosis involving subcutaneous and fascial tissue was determined to be 43.7% in the right corner, 28.1% in the left corner, 9.4% in the midline, and 18.8% within the rectus muscle. The time elapsed between cesarean section and the onset of symptoms was found to be statistically significantly shorter in patients who had undergone two or more cesarean sections compared to those with only one previous cesarean section (p=0.015).

Conclusion: Scar endometriosis is a painful condition for which clear success in medical treatment has not yet been demonstrated, and surgical intervention is often required. Given the higher frequency of occurrence at the corners of cesarean section incisions, we recommend the careful washing of these corners. Further immunohistochemical studies are needed to achieve success in medical treatment, and histopathological analysis should be fully elucidated.

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Introduction

Endometriosis is the presence of endometrial tissue (gland and stroma) outside the uterus.[1] It is observed in 5-10% of women of reproductive age and in 20-30% of infertile women.[2,3] Scar endometriosis (SE), on the other hand, is quite rare, developing in 0.2-0.4% of women following obstetric or gynecological surgeries.[4]

Various theories or combinations of these theories have been proposed to explain the pathogenesis of SE. The first suggests direct implantation of endometrial tissue into the scar tissue formed during surgery. The coelomic metaplasia theory proposes that a primitive pluripotent mesenchymal cell can differentiate to form endometrial cells under specific conditions. The combination of these theories suggests that under appropriate hormonal stimulation, cells that are directly implanted proliferate and can lead to scar endometriosis by inducing metaplasia in adjacent tissue.[4,5]

SE typically manifests as a nodule along the incision line and, although nonspecific, presents as a mass associated with cyclic pain related to menstruation along the incision line. Due to its lack of characteristic symptoms and its location, diagnosis may be delayed. It can often be confused with incisional hernia, abscess, or suture granuloma.[6,7] Ultrasonography (US), Computed Tomography (CT), and Magnetic Resonance Imaging (MRI) can assist clinicians, but diagnosis should be confirmed by histological examination.[6]

The aim of our study is to share our clinical experiences regarding scar endometriosis, which is becoming more common due to increasing cesarean operations, and to contribute to the literature on this subject.

Material and Methods

Our study included 32 patients who underwent surgery due to scar endometriosis at the Department of Gynecology, Ankara City Hospital, between September 2019 and September 2023. Ethics committee approval was obtained from the Clinical Research Ethics Committee of Ankara City Hospital (23/4491).

Our study is a comprehensive retrospective study in which patient records, operative notes, and pathology results were scanned from our hospital's electronic file archive. The age, parity, mode of delivery, number of previous cesarean sections, presented complaints, known history of pelvic endometriosis, physical examination findings at outpatient clinic visits, CA 125 values, size and location of the lesion determined by imaging methods, and the presence of pelvic endometriosis were recorded. The length of hospital stay after scar endometriosis surgery, postoperative complications, and histopathological results were obtained. If medical treatment was administered for scar endometriosis either before or after the operation, information on medical treatment and recurrence was noted, and all data was analyzed.

Statistical analyses were conducted using SPSS version 28. The normality of variables was examined visually (histograms and probability plots) and analytically (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyses were provided for variables showing normal distribution using mean and standard deviations. For parametric data determined to have normal distribution based on the Levene test, means were compared using the Student's t-test. The Mann-Whitney U test was used to compare non-normally distributed parametric and ordinal data. Categorical data was compared using appropriate methods such as the Chi-square or Fisher's exact test (in cases where the assumptions of the Chi-square test were not met in cell counts). Cases with a p-value less than 0.05 were considered statistically significant.

Results

All 32 patients included in the study had a history of at least one cesarean section, and their most recent surgeries were cesarean sections. Symptoms appeared after cesarean delivery in all patients. Surgical excision with clear margins was performed for all patients (including cases of recurrent scar endometriosis), and the pathological diagnosis for each excised lesion was endometriosis. The basic characteristics of the patients are summarized in Table 1. The mean age of the patients was 34.81±6.52 years, and all of them had undergone cesarean section with a Pfannenstiel incision. In all scar endometriosis lesions except those involving the rectus muscle, subcutaneous and fascial tissues were involved together. Subcutaneous and fascial involvement was found to be 43.7% in the right corner, 28.1% in the left corner, 9.4% in the midline, and 18.8% within the rectus muscle. Compared to other locations, scar endometriosis tissue located within the rectus muscle had larger dimensions, reaching 37±15.62 mm. Recurrence after surgery and resection with repeat surgery were detected in 4 patients. One patient had a concurrent history of endometrioma (Table 1).

Table 1. The demographic and clinical characteristics of patients undergoing scar endometriosis surgery

	N=32
Age (years)	34.81± 6.52
Parity	1.87± 0.79
Previous cesarean sections	5 (46.9%)
One Caesarean section	14 (43.7%)
Two Caesarean sections	3 (9.4%)
Three or more Caesarean sections	
Time from cesarean section until the onset of complaints (months)	29.4± 15.26
Time between the onset of the complaint and scar surgery (months)	16.43± 14.53
Complaint	30 (93.7%)
Pain	25 (78.1%)
Cyclic	5 (15.6%)
Continuous	2 (6.3%)
None	32 (100%)
Palpable mass	
Presence of previous or concurrent pelvic endometriosis	1 (3.1%)
Location of lesion	
Subcutaneous and Fascia Right	14 (43.7%)
Subcutaneous and Fascia Left	9 (28.1%)
Subcutaneous and Fascia Midline	3 (9.4%)
Within the rectus muscle	6 (18.8%)
Ultrasound size of the lesion (mm)	28.81± 10.25
Subcutaneous and Fascia Right	27.14± 9.23
Subcutaneous and Fascia Left	25.44± 5.02
Subcutaneous and Fascia Midline	30.33± 9.5
Within the rectus muscle	37±15.62
Duration of hospital stay (days)	2.4± 1.01
Presence of recurrence	4 (12.5%)
The pathological size of the lesion removed postoperatively (mm)	40.78± 13.97
CA 125 Values	21.09±15.25

The data is presented as mean±standard deviation and numerically (%)

The patients were divided into two groups: those who had undergone one cesarean section and those who had undergone two or more cesarean sections. The time elapsed between cesarean section and the onset of symptoms was found to be 23.13±15.82 months in patients with one previous cesarean section, while it was 10.53±10.54 months in patients who had undergone two or more cesarean sections, and it was statistically significantly shorter in patients who had undergone two or more cesarean sections (p=0.015) (Table 2).

Table 2. Comparison of scar endometriosis findings between patients who have undergone one cesarean section and those who have undergone two or more cesarean sections

	1 previous cesarean section (n= 15)	2 or more previous cesarean sections (n=17)	P value
Age	34.93±6.16	34.7±7.01	0.924
Time from cesarean section until the onset of complaint (months)	23.13±15.82	10.53±10.54	0.015*
Time between the onset of the complaint and scar surgery (months)	34.07±17.62	25.29±11.88	0.116
Complaint (Pain)			
Cyclic	12 (80%)	13 (76.5%)	
Continuous	2 (13.3%)	3 (17.6%)	0.944
None	1 (6.7%)	1 (5.9%)	
Location of lesion			
Subcutaneous and Fascia Right	5 (33.4%)	9 (53%)	
Subcutaneous and Fascia Left	6 (40%)	3 (17.6%)	0.392
Subcutaneous and Fascia	2 (13.3%)	1 (5.9%)	
Midline	2 (13.3%)	4 (23.5%)	
Within the rectus muscle			
Ultrasound size of the lesion (mm)	27.2±10.98	30.24±9.67	0.412
Duration of hospital stay (days)	2.33±0.61	2.47±1.28	0.708
The pathological size of the lesion removed postoperatively (mm)	39±10.38	42.35±16.68	0.129
CA 125 Values	25.33±20.54	17.35±7.04	0.171

The data is presented as mean±standard deviation and numerically (%). P<0.05 was considered statistically significant.

Discussion

In our clinic, all 32 patients who underwent surgery due to scar endometriosis had a history of previous cesarean section, although not statistically significant, the highest involvement was detected in the subcutaneous and fascial tissue in the right corner (43.7%). Compared to other locations, the scar endometriosis tissue located within the rectus muscle reached larger dimensions. Symptoms of scar endometriosis started statistically significantly earlier in patients with a history of 2 or more previous cesarean sections (p=0.015).

Studies have largely demonstrated the association of scar endometriosis cases with previous cesarean sections. The reason for this is best explained by the theory of direct implantation. In many patients with SE, as in our study, there is no history or evidence of pelvic endometriosis; this supports the theory that SE occurs as a result of the implantation of endometrial cells into the incision line during surgery, especially in cases with previous cesarean sections.[6] Compared to other gynecological opera-

tions, cesarean sections expose endometrial tissue more and subject it to trauma. Consequently, endometrial cells are implanted into surrounding tissues and proliferate. They are rarely detected, especially in subcutaneous and fascial tissue, and occasionally in the rectus muscle.[8] Zhang et al. presented 198 cases of cesarean scar endometriosis and found that lesions typically occurred at the corners of incision scars. They attributed this to the difficulty of removing endometrial cells from the corners of incisions during cesarean sections and suggested that corners should be more carefully cleaned during cesarean sections.[8] In our study, scar endometriosis tissue was particularly detected at a higher rate in the right corner of the incision line. While it may vary depending on which hand the surgeon uses, operations are generally performed from the patient's right side. Therefore, we believe that the incision corner on the side of the operating surgeon remains in a blind area and is not adequately cleaned due to insufficient visualization.

In scar endometriosis, patients typically present with cyclic pain and palpable mass complaints.[9] In our study, 78.1% of patients complained of cyclic pain, 15.6% of continuous pain, and all patients presented with a palpable mass complaint. Ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) are useful for diagnostic imaging.[9] While MRI and CT are useful in clarifying the size of the lesion, fascial involvement and the depth of lesion invasion, ultrasonography may be initially preferred due to its lower cost and demonstrated sufficiency in diagnosis.[10] In our study, patients underwent ultrasonographic imaging and no significant difference was found between the lesion sizes measured ultrasonographically and those resected with a safe surgical margin. Therefore, we believe that ultrasonography is useful in evaluating the size and invasion of the lesion. Additionally, although not statistically significant in our study, we found that scar endometriosis located within the rectus muscle tended to reach slightly larger sizes compared to those located subcutaneously. We think this may be due to increased vascularity in the muscle tissue and the depth of the tissue, which may not be palpable early on.

In one study, the time until scar endometriosis symptoms appeared after cesarean section was found to be 12.0 months (range: 19.0-39.0),[11] while in another study, this period was determined to be 31.6±23.9 months8. In our study, this period was 29.4±15.26 months. When patients were divided into two groups based on whether they had undergone two or more cesarean sections or only one, we found that symptoms of scar endometriosis appeared earlier in patients who had undergone two or more cesarean sections ($p=0.015$). No significant differences were found between these two groups in terms of lesion location, lesion size, or hospitalization duration. However, Zhang et al. were unable to find a significant difference between the number of previous cesarean sections and this period.[8] This may be due to the rapid growth of a small number of endometrial cells implanted into the incision scar after one cesarean section, leading to symptoms developing more quickly during the second and subsequent cesarean sections due to increased exposure to endometrial tissue. Studies have shown that scar endometriosis occurs in reproductive-aged women after cesarean section.[12] The average age in our study was 34.81±6.52, and the patients were in the reproductive period. Therefore, it is thought that the growth of scar endometriosis tissue is hormone-dependent. However, in previous studies, it has been found that hormonal treatments do not lead to changes in lesion size.[13] In a prospective study conducted by Seckin et al., patients were given dienogest, and although there was some reduction in pain, no change in lesion size was observed.[14] Dwivedi et al. conducted immunohistochemical studies on endometriosis tissue removed from surgical incision areas and found CK7 and CD10 positivity in this tissue.[15] Another study has shown that miRNA expressions in scar endometriosis tissue are different.[16] In this case, the presence or activity of estrogen receptors in scar endometriosis tissue and the absence or passivity of progesterone receptors may be considered. Another theory is that some proteins, antigens, and miRNA expressions found in scar endometriosis tissue may reduce the response to hormonal treatment. These theories need to be supported by further pathological immunohistochemical studies for confirmation. However, according to current literature, the first choice in treatment is surgical excision instead of hormonal treatment.[17] In our clinical practice, we also prefer surgical treatment over medical treatment in cases of scar endometriosis. There are also studies reporting that ultrasound-guided and magnetic resonance-guided high-intensity focused ultrasound are effective and safe in the treatment of abdominal wall endometriosis.[18] Howe-

ver, more randomized controlled studies are needed to clearly demonstrate this new treatment method. The postoperative recurrence rate in scar endometriosis has been reported as 4.5%-11.2%.[19] In our study, recurrence was detected in 4 patients (12.5%). Additionally, there are publications indicating a slight risk of malignancy in scar endometriosis. Although the disease evolves slowly (with an average time of 19.3 years between the initial surgery and the diagnosis of endometriotic malignant transformation), scar endometriosis has been reported to have a very poor prognosis for malignant transformation, with clear cell carcinoma being the most common (66.7%).[20] Therefore, it is recommended to excise the lesion with an appropriate margin of resection according to the extent of the lesion.

The strength of our study is its comprehensive nature, demonstrating a long period in a tertiary center. However, the retrospective design and the lack of immunohistochemical studies in the tissue are limitations of our study.

Conclusion

In conclusion, scar endometriosis following cesarean sections is becoming an increasingly serious health concern with the rising incidence of cesarean deliveries. The scar endometriosis can be seen earlier and more severely in cases with multiple C/S and it is seen more frequently in the right corner, which is the side of the primary surgeon. Based on the implantation theory, we recommend careful washing of the incision corners during cesarean sections to prevent scar endometriosis formation, and the use of separate needles for closing the uterus, fascia, and abdominal wall. We emphasize the importance of complete excision of the lesion with a clean surgical margin during scar endometriosis surgery to prevent recurrence. In order for scar endometriosis treatment to be carried out with non-invasive medical therapy, further immunohistochemical studies are needed to fully elucidate the histopathology of scar endometriosis.

Statements and Declarations

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Author contributions: All authors contributed to the study conception and design. İnci Halilzade: Conceptualization, Writing – original draft. Elçin İşlek Seçen: Data curation. Gonca Türker Ergün: Formal analysis. Ayşe Filiz Yavuz: Supervision. The first draft of the manuscript was written by [İnci Halilzade] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1. Nisolle M, Alvarez ML, Colombo M, Foidart JM. [Pathogenesis of endometriosis]. Gynecol Obstet Fertil. 2007; 35: 898-903.
2. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. Am J Epidemiol. 2004; 160: 784-796.
3. Prescott J, Farland LV, Tobias DK et al. A prospective cohort study of endometriosis and subsequent risk of infertility. Hum Reprod. 2016; 31: 1475-1482.
4. Nominato NS, Prates LF, Lauar I, Morais J, Maia L, Geber S. Caesarean section greatly increases risk of scar endometriosis. Eur J Obstet Gynecol Reprod Biol. 2010; 152: 83-85.
5. Uzuncakmak C, Guldas A, Ozcam H, Dinç K. Scar endometriosis: a case report of this uncommon entity and review of the literature. Case Rep Obstet Gynecol. 2013; 2013: 386783.
6. Buscemi S, Maiorana A, Fazzotta S et al. Scar endometriosis: not a rare cause for a painful scar. Clin Ter. 2021; 172: 129-133.
7. Horton JD, Dezee KJ, Ahnfeldt EP, Wagner M. Abdominal wall endometriosis: a surgeon's perspective and review of 445 cases. Am J Surg. 2008; 196: 207-212.
8. Zhang P, Sun Y, Zhang C et al. Cesarean scar endometriosis: presentation of 198 cases and literature review. BMC Womens Health. 2019; 19: 14.
9. Hirata T, Koga K, Osuga Y. Extra-pelvic endometriosis: A review.

Reprod Med Biol. 2020; 19: 323-333.
10. YoussefAT.Theultrasoundofsubcutaneousextrapelvicendometriosis.JUltrason.2020;20:e176-e180.
11. Pas K, Joanna SM, Renata R, Skręt A, Barnaś E. Prospective study concerning 71 cases of caesarean scar endometriosis (CSE). J Obstet Gynaecol. 2017; 37: 775-778.
12. Benedetto C, Cacozza D, de Sousa Costa D et al. Abdominal wall endometriosis: Report of 83 cases. Int J Gynaecol Obstet. 2022; 159: 530-536.
13. Durairaj A, Sivamani H, Panneerselvam M. Surgical Scar Endometriosis: An Emerging Enigma. Cureus. 2023; 15: e35089.
14. Seckin KD, Kadirogullari P. Is dienogest a convenient treatment option for cesarean scar endometriosis or should it be treated surgically? Eur J Obstet Gynecol Reprod Biol. 2023; 282: 110-115.
15. Dwivedi U, Shukla S, Anand N, Parashar C, Husain N. Scar Endometriosis: Cytological Diagnosis. JNMA J Nepal Med Assoc. 2018; 56: 550-552.
16. Szubert M, Nowak-Gluck A, Domanska-SenderowskaDetal.miR31-3pHasttheHighestExpressionin Cesarean Scar Endometriosis. Int J Mol Sci. 2022; 23.
17. Carsote M, Terzea DC, Valea A, Gheorghisan-Galateanu AA. Abdominal wall endometriosis (a narrative review). Int J Med Sci. 2020; 17: 536-542.
18. Knorren ER, de Ridder LA, Nijholt IM et al. Effectiveness and complication rates of high intensity focused ultrasound treatment for abdominal wall endometriosis: A systematic review. Eur J Obstet Gynecol Reprod Biol. 2024 Mar 26;297:15-23.
19. Marras S, Pluchino N, Petignat P et al. Abdominal wall endometriosis: An 11-year retrospective observational cohort study. Eur J Obstet Gynecol Reprod Biol X. 2019; 4: 100096.
20. Mihailovici A, Rottenstreich M, Kovel S, Wassermann I, Smorgick N, Vaknin Z. Endometriosis-associated malignant transformation in abdominal surgical scar: A PRISMA-compliant systematic review. Medicine (Baltimore). 2017; 96: e9136.

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RESEARCH ARTICLE

Effects of cesarean section duration on inflammation and postoperative parameters, a retrospective analysis

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Abstract

Introduction: Cesarean section it is the most frequently applied surgical application. Every surgical procedure creates an inflammation. Neutrophil to lymphocyte ratio (NLR), which can be easily obtained from complete blood count, is used as subclinical systemic inflammatory markers. In this study, our aim is to understand the effect of the duration of the cesarean section on subclinical inflammation by looking at the neutrophil/lymphocyte ratio and the effect of this period on blood loss and postoperative recovery

Methods: We included a total of 188 operations between the ages of 18-45 in our study and created 2 groups according to the duration of the cesarean section. When grouped as short (0-39 min) and long (≥40 min) according to the operation time, NOL change was higher in the group with longer operation duration, but no significant difference was found in both groups. Similarly, although the decrease in hemoglobin was higher in the group with a long operation time, no significant difference was found. No difference was observed between the two groups in terms of wound healing on the postoperative 10th day. When we look at our other parameters, we found a significant relationship between those whose cesarean section ended within 40 minutes and those who had their first cesarean section.

Results: As a result of our study, we could not detect a significant difference in the duration of the cesarean section operations performed in our clinic on the postoperative parameters.

Conclusion: Although supportive studies are needed, it shows that the surgical rules of cesarean section operate correctly under optimal conditions.

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Introduction

Cesarean section was an operation performed in the early 1900s to save women's lives. Today, it is the most frequently applied surgical application.[1] Every surgical procedure creates an inflammation. Inflammation is the immune system's response to endogenous or exogenous stimuli, which is essential but non-specific for the continuation of life. The reason for this response is to repair the cellular damage caused by the stimulus, to eliminate the cells and foreign substances, and to prevent the harmful effects on the organism by limiting the stimulus. There can be many infectious (gram-positive and gram-negative bacteria, virus, fungus, parasite, etc.) or non-infectious (trauma, burn, foreign body, ischemia, etc.) reasons for triggering inflammation.[2] Inflammation can be created by several causes, such as a blood clot that induces an ischaemic stroke; an immune system disorder; a cancer; a chemical exposure from polycyclic aromatic hydrocarbons, dioxin, smoking, etc; a physical injury including trauma or a haemorrhagic stroke; or a neurological condition, such as Alzheimer's disease, depression, etc.[3-7] Many infections by viral, bacterial, fungal and protozoan pathogens can cause inflammation.[8] The mechanism of inflammation; It is characterized by increased blood flow as a result of first vasoconstriction and then vasodilation in the vascular bed, separation of plasma proteins and leukocytes from the circulation as a result of structural changes in the microcirculation, migration and proliferation of leukocytes to the microcirculation, activation of complement, coagulation activation system and chemical mediators.[9]

Neutrophils; It is the most abundant cell group in the circulation and the first to go to the site of infection and inflammation. These cells migrate by being affected by chemotactic agents (interleukin-8, leukotriene B4, etc.) released from the area of inflammation. All of these chemoattractants diffuse from the site of infection or injury to provide a chemotactic gradient for the migration of neutrophils and further activate neutrophils during transmigration.[10-12]

In recent years, it has been shown that the ratio of neutrophil count to lymphocyte count (NOL) can be an indicator of systemic inflammation and is associated with prognosis in many cardiovascular diseases, malignancies and chronic inflammatory diseases.[13] Neutrophil to lymphocyte ratio (NLR), which can be easily obtained from complete blood count, is used as subclinical systemic inflammatory markers.

In this study, our aim is to understand the effect of the duration of the cesarean section on subclinical inflammation by looking at the neutrophil/lymphocyte ratio and the effect of this period on blood loss and postoperative recovery.

Material and Methods

We retrospectively analyzed the cesarean section operations performed in Kırıkkale university medical faculty hospital, gynecology and obstetrics clinic in 2020 and recorded by anesthesiologist. The study was carried out after the approval of the local ethics committee (Date of 19.04.2023 and 2023.03.01 decision no.) in Kırıkkale university medical faculty. We included a total of 188 operations between the ages of 18-45 in our study. We excluded the cases with any additional disease and complications during the cesarean section. We created 2 groups according to the duration of the cesarean section. The first group was operated within 40 minutes (n1=91), the second group was operated for more than 40 minutes (n2=97). We compared these two groups in terms of the neutrophil-lymphocyte ratio at the postoperative 24th hour, the difference in hemoglobin hematocrit values before and after the operation, and the wound healing on the 10th postoperative day.

We performed the statistical analysis in SPSS (Statistical Package for Social Sciences) program. Pearson correlation coefficient was used to compare numerical variables, Spearman test and Chi-square tests were used to compare categorical variables. Statistical significance was considered with p values <0.05.

Results

In our study, in which we retrospectively analyzed 188 cesarean section operations, we also analyzed the cases such as age, gestational week, number of pregnancies, whether they had a previous cesarean section or not.

Table 1: There was no statistically significant difference between the groups' age, number of pregnancies, gestational week, preoperative and postoperative NLR and Hb values, and NLR and Hb changes according to the duration of the operation (t-test was performed in independent groups) - All distributions are non-parametric

Table 1

	<40 minutes	≥ 40 minutes	
	Median	**Median**	***p***
Operation time	33	51	***0,000***
Age	28	29	***0,282***
Gravida	2	3	***0,017***
Gestasyonel week	37+6	37+4	***0,212***
Preop NLR	5,1	5,1	***0,962***
Postop NLR	7,5	7,0	***0,430***
Delta NLR	-2,3	-1,9	***0,516***
Preop Hb	12,0	11,6	***0,093***
Postop Hb	10,4	10,1	***0,141***
Delta Hb	1,5	1,4	***0,620***

Our operation times are distributed between 20 minutes and 114 minutes, with an average time of 41.9 minutes and a median time of 40 minutes. 65 of our cases had undergone cesarean section before and it was the first cesarean section of 123 of our cases. Average age is 28, average gestational week is 37+5. We found the mean preoperative NLR=5.12, post-operative mean NLR: 7.23, pre-operative median HG: 11.8 g/dl, post-operative median HG: 10.3 g/dl.

We statistically analyzed the differences in neutrophil-lymphocyte ratios and hemoglobin in the hemogram panel of our groups before and after the operation at the 24th hour. When grouped as short (0-39 min) and long (≥40 min) according to the operation time, NOL change was higher in the group with longer operation duration, but no significant difference was found in both groups (p=0.330). Similarly, although the decrease in hemoglobin was higher in the group with a long operation time, no significant difference was found (p=0.932). No difference was observed between the two groups in terms of wound healing on the postoperative 10th day.

When we look at our other parameters, we found a significant relationship between those whose cesarean section ended within 40 minutes and those who had their first cesarean section(P=0.35).

Discussion

In our study in which we compared the subclinical inflammation, wound healing and blood loss parameters of the duration of the cesarean section; we thought that subclinical inflammation would increase as the duration of cesarean section was prolonged, as the duration of exposure to trauma and open wound air contact lengthened.

In 2017, Hang Cheng et al. in their study titled " Prolonged Operative Duration Increases Risk of Surgical Site Infections(SSI): A Systematic Review(14)"; concluded " prolonged operative time can increase the risk of SSI. Given the importance of SSIs on patient outcomes and health care economics, hospitals should focus efforts to reduce operative time". However, in our study, we could not detect that subclinical inflammation increased with the prolongation of the operation time by looking at the NLR and wound healing evaluations. Operative time is an independent risk factor for SSI, which may be partially modifiable, unlike some patient risk factors such as diabetes mellitus. There are many parameters that can influence operative time, including preoperative planning, surgeon experience, surgeon fatigue, operating room staff experience and access to equipment. The exact mechanisms by which the incidence of SSI increases due to increased operative time are not fully understood, but several studies suggest plausible reasons. With increasing operative time, patients' open incisions are exposed to the environment for longer, which increases the risk of bacterial contamination. Longer operative time predisposes incisions to tissue drying, which may also increase the likelihood of contamination.[15,16] Longer operative times may also mean increased surgical team fatigue and room for more technical errors.[17,18,19] Moreover, longer operative times often represent more complex surgical procedures.[15] Some of the factors that increase operative time can be modified while others may not. In any case, measures that can help reduce operative time and optimize workflow should be used. In patients with longer targeted or unexpected operative times, strict adherence to infection prevention measures is essential.[16,20] Studies have reported that intra-procedural antibiotic dosing may be cost-effective in higher-risk patients.[21] Although surgical procedures should not be unnecessarily shortened, many avoidable factors can cause delays. Familiarity of the surgical team

with the procedure and equipment should be addressed prior to the procedure. Preoperative planning can help reduce the time spent on intraoperative decision-making and predict material requirements.[22] The design of device implants or instruments can help minimize the number of steps required in the procedure.[23,24] It can also serve as an indicator or guideline for the standard, expected operative time, surgical quality and associated risk of complications for a given surgery. In a study reporting expected OR time across various surgeries, procedures longer than the expected OR time (i.e., greater than 95% CI of the expected OR time) were found to carry a significantly greater risk of complications, whereas procedures with shorter than expected duration were found to have a lower risk of postoperative events.[25] In summary, planning, procedure efficiency, and surgeon training should be optimized to minimize the impact of operative time on the incidence of SSI whenever possible.[26]

We could not detect a relationship between operation time and blood loss. When we look at the literature, we did not see a study similar to ours.

The reason why we did not find a difference in terms of inflammation in cesarean section operations in our study may mean that surgical sterilization rules and antibiotic prophylaxis were fully followed.

We may not have been able to detect a difference between groups in terms of inflammation markers in our study, since pregnancy and childbirth itself already increase inflammation markers.

It can be considered critically that the organization of the time groups in our study was not to such an extent that it would affect the NLO.

When we look at the other parameters in our study, we found that the operation time was shorter in cases with the first cesarean section, which is a known fact that tissue adhesions slow down the operation in those who have had a previous cesarean section.

Conclusion

As a result of our study, we could not detect a significant difference in the duration of the cesarean section operations performed in our clinic on the postoperative parameters. Although supportive studies are needed, it shows that the surgical rules of cesarean section operate correctly under optimal conditions.

Disclosure statement

No potential conflict of interest was reported by the authors

References

1) Dölen İ, Özdeğirmenci Ö. Kadın Doğum Hekimliğinde Etik ve Yasal Sorunlar (Yeni düzenlemeler) Ed: Çiçek MN, Akyürek C, Çelik Ç, Haberal A. Güneş Kitabevi, 2006:155-164

2) Roe K. An inflammation classification system using cytokine parameters. Scand J Immunol. 2021 Feb;93(2):e12970. doi: 10.1111/sji.12970. Epub 2020 Sep 18. PMID: 32892387.

3) Doll DN, Barr TL, Simpkins JW. Cytokines: their roles in stroke and potential use as biomarkers and therapeutic targets. Aging Dis. 2014; 5(5): 294-306.

4) Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease. Int J Mol Sci. 2019; 2: 6008.

5) Francescone R, Hou V, Grivennikov SI. Cytokines, IBD and colitis-associated cancer. Inflamm Bowel Dis. 2015; 21(2): 409-418.

6) Lecureur V, Le Ferrec E, N'diaye M, et al. ERK-dependent induction of TNFα expression by the environmental contaminant benzo(a)pyrene in primary human macrophages. FEBS Lett. 2005; 579(9): 1904-1910.

7) Reikeras O, Borgen P, Reseland JE, Lyngstadaas SP. Changes in serum cytokines in response to musculoskeletal surgical trauma. BMC Res Notes. 2014; 7: 128.

8) Banerjee A, Khemka VK, Roy D, et al. Role of pro-inflammatory cytokines and vitamin D in probable Alzheimer's disease with depression. Aging Dis. 2017; 8(3): 267-276.

9) Prasad S, Tyagi AK, Aggarwal BB. Detection of inflammatory biomarkers in saliva and urine: potential in diagnosis, prevention, and treatment for chronic diseases. Exp Biol Med. 2016; 241: 783-799.

10) Netea MG, Domínguez-Andrés J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. Nat Rev Immunol 2020; 20:375.

11) Rehaume LM, Hancock RE. Neutrophil-derived defensins as modulators of innate immune function. Crit Rev Immunol 2008; 28:185.

12) Nauseef WM. How human neutrophils kill and degrade microbes: an integrated view. Immunol Rev 2007; 219:88.

13) Berliner N, Coates TD. Introduction to a review series on human neutrophils. Blood 2019; 133:2111.

14) Telo S, Kuluöztürk M, Deveci F, Kirkil G. The relationship between platelet-to-lymphocyte ratio and pulmonary embolism severity in acute pulmonary embolism. Int Angiol. 2019 Feb 1;38(1):4– 9.

15) Cheng H, Chen BP, Soleas IM, Ferko NC, Cameron CG, Hinoul P. Prolonged Operative Duration Increases Risk of Surgical Site Infections:

A Systematic Review. Surg Infect (Larchmt). 2017 Aug/Sep;18(6):722-735. doi: 10.1089/sur.2017.089. PMID: 28832271; PMCID: PMC5685201.
16) Nguyen TJ, Costa MA, Vidar EN, et al.. Effect of immediate reconstruction on postmastectomy surgical site infection. Ann Surg 2012;256:326–333
17) Haridas M, Malangoni MA. Predictive factors for surgical site infection in general surgery. Surgery 2008;144:496–501
18) Li GQ, Guo FF, Ou Y, et al.. Epidemiology and outcomes of surgical site infections following orthopedic surgery. Am J Infect Control 2013;41:1268–1271
19) Bennett-Guerrero E, Welsby I, Dunn TJ, et al.. The use of a postoperative morbidity survey to evaluate patients with prolonged hospitalization after routine, moderate-risk, elective surgery. Anesth Analg 1999;89:514–519
20) Hoekstra LT, van Trigt JD, Reiniers MJ, et al.. Vascular occlusion or not during liver resection: The continuing story. Dig Surg 2012;29:35–42
21) Sessler DI, Akca O. Nonpharmacological prevention of surgical wound infections. Clin Infect Dis 2002;35:1397–1404
22) Enzler MJ, Berbari E, Osmon DR. Antimicrobial prophylaxis in adults. Mayo Clin Proc 2011;86:686–701
23) Willis-Owen CA, Konyves A, Martin DK. Factors affecting the incidence of infection in hip and knee replacement: An analysis of 5277 cases. J Bone Joint Surg Br 2010;92:1128–1133
24) Frecker MI, Powell KM, Haluck R. Design of a multifunctional compliant instrument for minimally invasive surgery. J Biomech Eng 2005;127:990–993
25) Daley BJ, Cecil W, Clarke PC, et al.. How slow is too slow? Correlation of operative time to complications: An analysis from the Tennessee Surgical Quality Collaborative. J Am Coll Surg 2015;220:550–558
26) Maoz G, Phillips M, Bosco J, et al.. The Otto Aufranc Award: Modifiable versus nonmodifiable risk factors for infection after hip arthroplasty. Clin Orthop Relat Res. 2015;473(2):453–9

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RESEARCH ARTICLE

Prenatal diagnosis and postnatal outcomes of cavum septum pellucidum et vergae

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Abstract

Introductıon: Evaluation of demographic characteristics and postnatal outcomes of fetuses with cavum septum pellucidum et vergae (CSPV) diagnosis followed in a tertiary center.

Methods: This retrospective study was conducted in Ankara Bilkent City Hospital perinatology clinic between 2020-2023. Cases with the prenatal diagnosis of CSPV were evaluated. Demographic features, prenatal ultrasound findings, noninvasive screening test results, invasive diagnostic test results, prenatal anomaly screening ultrasound findings, and postnatal outcomes were reported.

Results: There was a total of 24 prenatally diagnosed CSPV cases during the study period. The mean gestational week at diagnosis was 25.6 ± 3.2 weeks. Nineteen patients participated in noninvasive screening tests; five patients declined them. Noninvasive screening tests revealed low risk in 17 patients and high risk in 2. Amniocentesis was performed in 5 patients; 3 of them had a normal karyotype, 1 fetus was diagnosed with Smith-Lemli-Opitz syndrome, and 1 fetus had trisomy 21. Six patients with isolated CSPV were accepted and underwent fetal MRI, other eighteen patients refused MRI. MRI corrected the CSPV in all six patients, and they had no additional findings. Five (%21) fetuses were admitted to the intensive care unit because of recurrent absence convulsions (n=1), anal atresia (n=1), cleft lip palate (n=1), respiratory distress (n=1) and hypoplastic left heart syndrome (n=1).

Conclusion: CSPV is considered a normal variant of cavum septum pellucidum and can be diagnosed during ultrasound screening for fetal anomalies; in isolated cases perinatal outcomes are favorable.

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Introduction

The cavum septum pellucidum, which is considered a normal anatomical variation in the brain, is a potential space containing fluid between the membranous leaves in the frontal region.[1] The CSP is a structure situated between the medial border of the frontal horns and the bodies of the lateral ventricles. It is closely associated with the corpus callosum, which defines its rostral and superior boundaries. The body of the fornix constitutes its posterior-inferior floor. At 10 to 12 weeks of gestation, this developmental process initiates and achieves its adult form at 17th gestatioanal week, which which aligns with the formation of the corpus callosum.

The corpus callosum is located close to the CSP and defines its superior and rostral borders. The posterior and inferior aspects of the fornix are formed by its own body. The CSP is not merely a membrane; it does not contain organised grey matter either. The CSP consists of two sheaths of white matter located close to each other along the midline containing fibres.[2,3] The prenatal observation of CSP is a key indicator of proper foetal brain development. The prenatal observation of CSP is a key indicator of proper foetal brain development. Developmental anomalies of this midline space are strongly associated with the development of neuropathological disorders.[4,5] Although the exact function of the CSP remains unclear, it is hypothesised to be an essential element of the limbic system and to influence behaviours such as anger and arousal.[6]

Cavum septum pellucidum et vergae (CSPV) is an anatomical variant that forms the continuation of the posterior wall of the CSP. This variant forms an extension that extends beyond the walls of the fornix and the Monro foramines. About 30% of newborns have this variant, but only less than 1% of adults have this structure. CSP and CSPV have been observed in nearly all premature infants with normal brain architecture.[7] The midline anatomical structures initiate the process of closure in a posterior direction. It has been demonstrated that the cavum vergae is the first to close. Furthermore, it has been established that the closure of the CSPV commences in the sixth month of gestation.[8,9]

The objective of this study was to undertake a comparative analysis of the prenatal and postnatal characteristics and demographic data of fetuses diagnosed with CSPV at a tertiary care center.

Material and Methods

This is a retrospective observational study conducted between January 2021 and November 2023 in the perinatology clinic of a tertiary care hospital on cases with a diagnosis of CSPV. The study protocol received approval from the relevant institutional ethics committee (reference number E2-23-5191) and written informed consent was obtained from all participants prior to their involvement in the study. The following variables were recorded: demographic characteristics, antenatal ultrasound findings, results of non-invasive screening tests, results of invasive diagnostic tests, antenatal screening ultrasound findings regarding anomalies and postnatal outcomes. An ultrasound assessment was conducted by the same experienced perinatologist using a Voluson E10 with a 2-9 MHz abdominal convex probe. The assessment was initially conducted to screen for fetal anatomy at 20-24 weeks' gestation and subsequently repeated at two-week intervals until delivery to monitor the pregnancy.

A statistical analysis was performed utilising the SPSS 22 software, produced by IBM Corp. in New York. The Kolmogorov-Smirnov test was employed in order to ascertain whether the data exhibited a normal distribution. For variables exhibiting a normal distribution, mean and standard deviation were employed as descriptive statistics. In the case of non-normally distributed continuous variables, the median and range were employed as the statistical measures. Categorical variables were expressed as frequencies and relative percentages.

Results

The study period yielded a total of 24 identified cases of prenatal diagnosis of CSPV. A summary of the demographic characteristics and clinical presentation of all CSPV cases is provided in Table 1. On average, the gestational age at diagnosis was 25.6 ± 3.2 weeks. The mean age of the subjects included in the study was 28.4 ± 5.8 years. The median gravidity was 3 (range 1-8), and the median parity was 2 (range 0-7). The sex of 13 fetuses (54%) was male, and 11 (46%) were female.

Five patients refused prenatal screening. Prenatal screening tests were performed in nineteen patients. The non-invasive prenatal screening tests demonstrated that seventeen patients fell within the low-risk category for chromosomal abnormalities, while two patients were identified as being at a higher

risk. Amniocentesis was performed in five patients; three of them had a normal karyotype, 1 fetus was diagnosed with Smith-Lemli-Opitz syndrome and 1 fetus had trisomy 21. Although CSPV was an isolated finding on ultrasound in 18 (75%) of the foetuses, the remaining 6 (25%) foetuses exhibited additional anomalous findings on ultrasound. Additional fetal anomalies include a fetus with hypoplastic left heart syndrome (HSLS), a fetus with atrioventricular septal defect (AVSD), a fetus with anal atresia, a fetus with hemivertebra, ASD and single umbilical artery, a fetus with slight enlargement of the posterior lateral ventricle, and a fetus with cleft lip and palate.

Six patients with isolated CSPV were accepted and underwent fetal MRI, the other eighteen patients refused MRI. MRI confirmed CSPV in all six patients and they had no additional findings. Two pregnancies were terminated as a consequence of the presence of significant fetal anomalies or chromosomal abnormalities; one of the fetuses was terminated at 26 weeks' gestation because of Smith-Lemli-Opitz syndrome and the other at 24 weeks' gestation because of trisomy 21. Autopsies could not be performed due to lack of parental consent.

Table 1: Demographic features of Cavum Septum Pellucidum et vergae cases n=24

Maternal Age		28.4 ± 5.8
Gravidity		3 (1-8)
Parity		2 (0-7)
Gestational age at diagnosis (week)		25.6 ± 3.2
Noninvasive screening test	High risk	2
	Low risk	17
	Refused	5
Amniosynthesis	performed (n=5)	Normal (3) Trisomy 21 (1) Smith-Lemli-Opitz Syndrome (1)
Fetus gender	Male	13 (%54)
	Female	11 (%46)
MRI	Normal	6
	Abnormal	0
CSPV as an isolated finding		18 (%75)
CSPV with additional anomalies*		6 (%25)

* Additional anomalies were: hypoplastic left heart syndrome, atrio-ventricular septal defect, anal atresia, hemivertebrae, ASD and single umbilical artery, dilatation of the right lateral ventricle (12 mm), cleft lip and palate

A summary of the short-term postnatal outcomes of CSPV live births is provided in Table 2. The mean gestational age of the remaining 22 fetuses was 37.2 ± 1.6 weeks. The mean birth weight was 2972 ± 586 grams. The mean Apgar scores for the fetuses were 7 (range 5-8) at one minute and 8 (range 6-9) at five minutes. A total of five fetuses (22.7%) were admitted to the neonatal intensive care unit (NICU). One for recurrent absence seizures (n=1), one for anal atresia (n=1), one for hypoplastic left heart syndrome (n=1), one for cleft lip palate (n=1) and one for respiratory distress (n=1). All infants born alive were followed up by a paediatrician and a developmental-behavioural paediatrician for a period of two years. At follow-up, isolated and chromosomally normal CSPV cases have normal neurological and physical development for their age.

Table 2: Postnatal outcomes of Cavum Septum Pellucidum et vergae cases (n=22)

Birth week	37.2 ± 1.6
Birth weight (gram)	2972 ± 586
Apgar score 1st minute (range)	7 (5-8)
Apgar score 5th minute (range)	8 (6-9)
NICU admission*	5(%27.7)

NICU: neonatal intensive care unit
* Recurrent absance seizures (n=1), cleft lip palate (n=1), hypoplastic left heart syndrome(n=1), respiratory distress (n=1) and anal atresia (n=1).

Discussion

According to this study, favourable outcomes were observed in the majority of CSPV cases. While prenatal diagnosis of fetal CSPV can prove challenging, detection rates have increased with the advent of more sophisticated imaging technologies and the accumulating experience in maternal-foetal medicine. Given our limited knowledge of the prognosis of prenatally detected cases, studies focusing on this specific topic may be useful to guide clinicians in providing accurate information to parents.

In a prospective study of 322 low-risk pregnancies, the frequency of CSPV and the morphological findings of CSP were investigated. In this study, the incidence of CSPV was found to be 7.2%. This study highlights the common morphological features of CSPV and the fact that CSPV is present in a significant proportion of clinically normal fetuses.[10]

In a prospective observational study conducted at a single centre involving 11,200 pregnant women, the frequency of CSPV was assessed through the utilisation of prenatal ultrasound, resulting in the detection of eight fetuses within this cohort. Anomalies were observed in five fetuses. Three of the five fetuses exhibited hydrocephalus, one displayed growth retardation, and one demonstrated a chromosomal abnormality (11/22 translocation). The pregnancy was terminated due to the presence of significant congenital anomalies and chromosomal anomalies in four fetuses. One neonate exhibited communication with the third ventricle of the CNS in accordance with the CSPV, while another demonstrated mild ventriculomegaly on postnatal ultrasound. The three surviving fetuses exhibited typical neurological development during the first months of life. The findings of this study indicate that isolated cases of CSPV may have normal neurological development, but it is crucial to consider the potential association with fetal malformations.[11]

In a retrospective single-center study evaluating 111 infants with confirmed 22q11.2 deletion (Di George Syndrome), magnetic resonance imaging (MRI) was performed on 24 infants who presented with neurological symptoms. MRI revealed that eight of the 24 infants exhibited persistent CSP and/or CSPV. The elevated prevalence of CSP and CSPV persistence indicates that the closure of these anatomical structures may be delayed or incomplete in chromosomal abnormalities. The findings revealed the types and frequencies of brain malformations observed in the case series, suggesting the prevalence of neuroanatomical anomalies in 22q11.2DS may be underestimated.[12] In contrast with the findings of recent studies, our investigation did not identify any patients with DiGeorge syndrome. It is hypothesised that this discrepancy can be attributed to the relatively limited patient population included in the study.

This retrospective case-control study involved the measurement of the length and width of the CSP in the axial plane of the fetal head, as defined by the CSP length/width ratio. The study included 323 normal fetuses and 20 fetuses with pACC between 20 and 34 weeks of gestation. In the general study population, the length and width of the CSP exhibited a positive correlation with increasing BPD, whereas the proportion of CSP demonstrated a negative correlation. In 85% (17/20) of foetuses with partial agenesis of the corpus callosum (pACC), the length of the CSP was below the 5th percentile, while in 65% (13/20) of cases, the width was below the 95th percentile. The CSP ratio was observed to be below the 5th percentile in 95% (19/20) of pACC foetuses, with 16/20 (80%) exhibiting a ratio that was below the empirically derived cut-off point of 1.5. A Z-score analysis demonstrated that foetuses with pACC exhibited a markedly diminished CSP rate in comparison to the control population ($p < 0.0001$).[13] As our study was retrospective and the CSP dimensions are not routinely recorded, we were unable to include the CSP ratio in our analysis.

Conclusion

The principal strength of our study is that we evaluate cavum vergae, a subject that has not been extensively researched to date and has been regarded as a variant of normal until now, from a novel perspective. The current study is constrained by its monocentric design and comparatively small sample size, which is derived from a single ethnic group. The findings of our study concur with those of previous research in that cavum results have an excellent prognosis in isolated cases.

The advent of improved ultrasound technology has led to a significant advancement in the field of prenatal diagnosis of fetal anomalies over the past decade. Prenatal diagnosis is a crucial aspect in cases such as CSPV, as early detection allows for the possibility of anatomical and genetic screening for associated anomalies, preparation for neonatal care and interventions, and comprehensive patient information. The findings of our study indicate that isolated and chromosomally normal CSPV cases exhibited normal neurological and physical development during follow-ups. The findings of the recent study are largely in alignment with those of previous research. Further research into prenatal diagnosis and perinatal outcomes in this context may yield valuable insights for clinicians, enabling early diagnosis and management of patients with CSPV.

Statements & Declarations

Informed consent

The rights of all participants were protected and written informed consent was obtained prior to procedures in accordance with the Declaration of Helsinki.

Conflicts of interest

The authors have no competing interests to declare.

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References

1. Nakajima Y, Yano S, Kuramatsu T, Ichihashi K, Miyao M, Yanagisawa M, et al. Ultrasonographic evaluation of cavum septi pellucidi and cavum vergae. Brain Dev. 1986;8(5):505–8.
2. Sarwar M. The septum pellucidum: normal and abnormal. Am J Neuroradiol. 1989;10(5):989–1005.
3. Rakic P, Yakovlev PI. Development of the corpus callosum and cavum septi in man. J Comp Neurol. 1968;132(1):45–72.
4. Winter TC, Kennedy AM, Byrne J, Woodward PJ. The cavum septi pellucidi: why is it important? J Ultrasound Med. 2010;29(3):427–44.
5. Malinger G, Lev D, Kidron D, Heredia F, Hershkovitz R, Lerman-Sagie T. Differential diagnosis in fetuses with absent septum pellucidum. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol. 2005;25(1):42–9.
6. Sitoh Y-Y, Tien RD. The limbic system. An overview of the anatomy and its development. Neuroimaging Clin N Am. 1997;7(1):1–10.
7. Mott SH, Bodensteiner JB, Allan WC. The cavum septi pellucidi in term and preterm newborn infants. J Child Neurol. 1992;7(1):35–8.
8. Pilu G, Sandri F, Perolo A, Pittalis MC, Grisolia G, Cocchi G, et al. Sonography of fetal agenesis of the corpus callosum: a survey of 35 cases. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol. 1993;3(5):318–29.
9. Jou H, Shyu M, Wu S, Chen S, Su C, Hsieh F. Ultrasound measurement of the fetal cavum septi pellucidi. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol. 1998;12(6):419–21.
10. Tao G, Lu G, Zhan X, Li J, Cheng L, Lee K, et al. Sonographic appearance of the cavum septum pellucidum et vergae in normal fetuses in the second and third trimesters of pregnancy. J Clin Ultrasound. 2013;41(9):525–31.
11. BRONSHTEIN M, WEINER Z. Prenatal diagnosis of dilated cava septi pellucidi et vergae: associated anomalies, differential diagnosis, and pregnancy outcome. Obstet Gynecol. 1992;80(5):838–42.
12. Bohm LA, Zhou TC, Mingo TJ, Dugan SL, Patterson RJ, Sidman JD, et al. Neuroradiographic findings in 22q11. 2 deletion syndrome. Am J Med Genet Part A. 2017;173(8):2158–65.
13. Karl K, Esser T, Heling KS, Chaoui R. Cavum septi pellucidi (CSP) ratio: a marker for partial agenesis of the fetal corpus callosum. Ultrasound Obstet Gynecol. 2017;50(3):336–41.

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RESEARCH ARTICLE

Effect of specific immunotherapy on plasma interleukin 13 and 8 levels in patients with allergic rhinitis

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Abstract

Introductıon: This study aimed to evaluate interleukin (IL)-13 and IL-8 levels in patients with allergic rhinitis who were and were not receiving specific immunotherapy.

Methods: A total of 84 patients being followed up in the immunology-allergy outpatient clinic for allergic rhinitis (42 receiving immunotherapy) and 23 healthy control subjects were included. Serum IL-13 and IL-8 levels were measured by enzyme-linked immunosorbent assay in all groups. Allergic rhinitis patients were also evaluated in terms of symptom scores, IgE levels, and skin prick test results.

Results: Comparison of serum IL-13 and IL-8 among the groups demonstrated that levels of both cytokines were significantly higher in both allergic rhinitis patient groups compared to controls ($p<0.001$), and significantly higher in symptomatic allergic rhinitis patients compared to patients receiving immunotherapy ($p<0.001$ for IL-13, $p=0.004$ for IL-8).

Conclusion: Immunotherapy is the only curative treatment for allergic rhinitis. The results of our study suggest that immunotherapy exerts its effect by modifying levels of IL-13 and IL-8 in addition to previously well-known cytokines.

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Introduction

Allergic rhinitis is one of the most common chronic diseases, affecting 10-40% of the entire population. Epidemiological data demonstrate an increase in its prevalence.[1,2] Although generally not a severe disease, it reduces quality of life and causes significant financial and labor loss.

Allergic rhinitis affects the nasal cavity and paranasal sinuses, manifesting as a complex of symptoms that includes sneezing attacks, itching of the nose and palate, rhinorrhea, and nasal congestion. Other symptoms such as eye itching and watering, postnasal discharge, decreased hearing, cough, and shortness of breath may also occur.[3,4]

As allergic rhinitis is a disease of atopic individuals, these patients may also have systemic allergic symptoms. The cause is an IgE-dependent type 1 hypersensitivity reaction, and symptoms occur as a result of the person's previous exposure to the IgE-inducing allergen. The IgE antibodies bind to receptors on mast cells in the respiratory mucosa and basophils in the peripheral circulation. Cross-linking of allergens to the IgE antibodies on the surface of these cells results in mast cells releasing preformed chemical mediators. These cells also produce other mediators and cytokines that cause the development of chronic symptoms due to nasal inflammation and continuous allergen exposure.[5,6]

Cytokines are regulatory proteins secreted by cells involved in both the specific and innate immune systems and are vital for immune system functions. Although cytokines are not antigen-specific, their production and secretion are dependent on antigen stimulation. They have different names because they originate from many different cells and exert different effects on different target cells.

Cytokines play a role in all stages of immune response and inflammation, including antigen presentation, immune cell differentiation, maturation, and activation, adhesion molecule expression, and acute phase response.[7,8] They also play an important role in the pathogenesis of allergic diseases. Based on these characteristics, in this study we examined changes in serum levels of the cytokines interleukin (IL)-8 and IL-13 in patients with allergic rhinitis who did and did not receive specific immunotherapy (SIT).

Material and Methods

The study included patients who presented to the immunology/allergy outpatient clinic in the internal medicine department of the Ministry of Health Dışkapı Training and Research Hospital and were diagnosed with allergic rhinitis by history, physical examination, laboratory, and skin tests. The patients were grouped into those who were not receiving SIT and were symptomatic (Group 1, n=42) and those who were receiving SIT (Group 2, n=42). The control group included healthy individuals with no known systemic diseases who were shown to have no allergic disease according to history, physical examination, and skin tests (n=23). The study was approved by the Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital, with the approval number 33/2009 and the date 19.03.2009.

Inclusion criteria; Patients aged ≤45 years diagnosed with allergic rhinitis by history, physical examination, laboratory, and skin tests. Healthy individuals aged ≤45 years were included in the control group. Exclusion criteria: Individuals with systemic diseases other than allergic rhinitis or those with incomplete clinical data were excluded from the study.

Morning fasting blood samples were collected from all subjects for measurement of IL-13, IL-8, and IgE levels. Serum was separated and stored at -70°C until analysis.

Skin prick tests with 48 allergens, including common aeroallergens (Stallergenes, In Vitro Allergy Diagnosis Kit, France), were performed on the forearm using standard needles with a 1.0-mm tip. Physiological saline solution was used as the negative control and 10 mg/mL histamine solution was used as the positive control. The results were evaluated after 15 minutes, and a wheal 10-15 mm in diameter (grade 3+) was accepted as a positive reaction.

In clinical trials for the treatment of allergic rhinitis, patients are often asked to keep a daily log of complaints and their severity. Considering that symptoms may differ between day and night, an extended symptom scoring format including nighttime symptoms (such as difficulty falling asleep, frequent waking) was used. In this scoring system, symptoms are rated by severity as none,⁰ mild but not disturbing.¹ moderate and occasionally disturbing,² severe and often disturbing.³ The symptom scores of our patients were assessed and recorded in follow-up visits.

eStallergenes APSI allergen extracts (France)

were administered as SIT. Injections were initially performed weekly. After reaching a certain dose (maintenance dose), this interval was extended to once every 15 days and later to once a month. Injections were administered subcutaneously over the deltoid muscle.

Serum IL-13 and IL-8 levels of the patients and control subjects were measured by enzyme-linked immunosorbent assay (ELISA). The ELISA tests for IL-13 and IL-8 levels were performed using the ELISA (Labsystem, Multi Skan EX, Finland) reader.

Statistical Analysis

When analyzing the data, the nonparametric Kruskal-Wallis H test was used for comparisons between multiple groups. This test only shows whether there is a difference between the groups. For this reason, there is no appropriate post-hoc test. Therefore, post-hoc pairwise comparisons were performed using the Mann-Whitney U test. Statistical analyses were performed using SPSS 14.0, with the Kruskal-Wallis H test used for comparing multiple groups, and the Mann-Whitney U test for post-hoc pairwise comparisons. A p value <0.05 was considered statistically significant.

Results

Group 1 included 30 women and 12 men with symptomatic allergic rhinitis who were not receiving SIT. Their age range was 21-45 years and the disease duration was 5-22 months. Group 2 included 28 women and 14 men with allergic rhinitis who were receiving SIT. They were 23-41 years of age, the disease duration was 8-23 months, and SIT duration was 40-52 months. The control group included 23 healthy individuals (13 female and 10 male) with an age range of 24-40 years (Table 1).

Table 1: Demographic characteristics of the allergic rhinitis patient and control groups

	No SIT (n=42)	SIT (n=42)	Controls (n=23)
Sex (n female/male)	30/12	28/14	13/10
Age (years)	32.5 ± 6.4	34 ± 4.6	31.7 ± 4.69
Disease duration (months)	11.64 ± 4.74	15.81 ± 4.01	-
SIT duration (months)	-	47.48 ± 2.39	-

SIT: Specific immunotherapy

In Group 1, it was determined that 17 patients were allergic to grasses, 7 to tree pollen, and 18 to house dust. The distribution of these allergy types was very similar in Group 2 (18 grass, 6 tree pollen, and 18 house dust allergies) (Table 2). Two-thirds of patients receiving SIT reported no symptoms of allergic rhinitis, while the remaining third had mild symptoms. All patients not receiving SIT had moderate to severe symptoms (Table 2).

Table 2: Clinical characteristics of the allergic rhinitis patient groups

Allergy Type	No SIT n (%)	SIT n (%)
Grass	17 (40.5)	18 (42.9)
Tree pollen	7 (16.7)	6 (14.3)
House Dust	18 (42.9)	18 (42.9)
Symptom Severity		
None	-	28 (66.7)
Mild	-	14 (33.3)
Moderate	21 (50)	-
Severe	21 (50)	-

SIT: Specific immunotherapy

The mean serum IL-13 level was 0.99±0.20 pg/dL in Group 1, 0.72±0.04 pg/dL in Group 2, and 0.57±0.15 pg/dL in the control group. Mean serum IL-8 levels in these groups were 1.07±0.12 pg/dL, 0.77±0.07 pg/dL, and 0.72±0.06 pg/dL, respectively. Statistical comparisons of serum IL-8 and IL-13 between the groups showed that levels of both cytokines were significantly higher in allergic rhinitis patients without SIT than in those with SIT and healthy controls (Table 3) (Figure 1).

Table 3: Comparison of cytokine levels in the allergic rhinitis patient and control groups

	No SIT1 (n=42)	SIT2 (n=42)	Controls3 (n=23)	p value
IL-13 (pg/dL), mean ± SD	0.99 ± 0.20	0.72 ± 0.04	0.57 ±0.15	<0.001, 1 vs. 2,3; <0.001, 2 vs. 3
IL-8 (pg/dL), mean ± SD	1.07 ±0.12	0.77 ±0.07	0.72 ± 0.06	<0.001, 1 vs. 2, 3; 0.004, 2 vs. 3

SIT: Specific immunotherapy

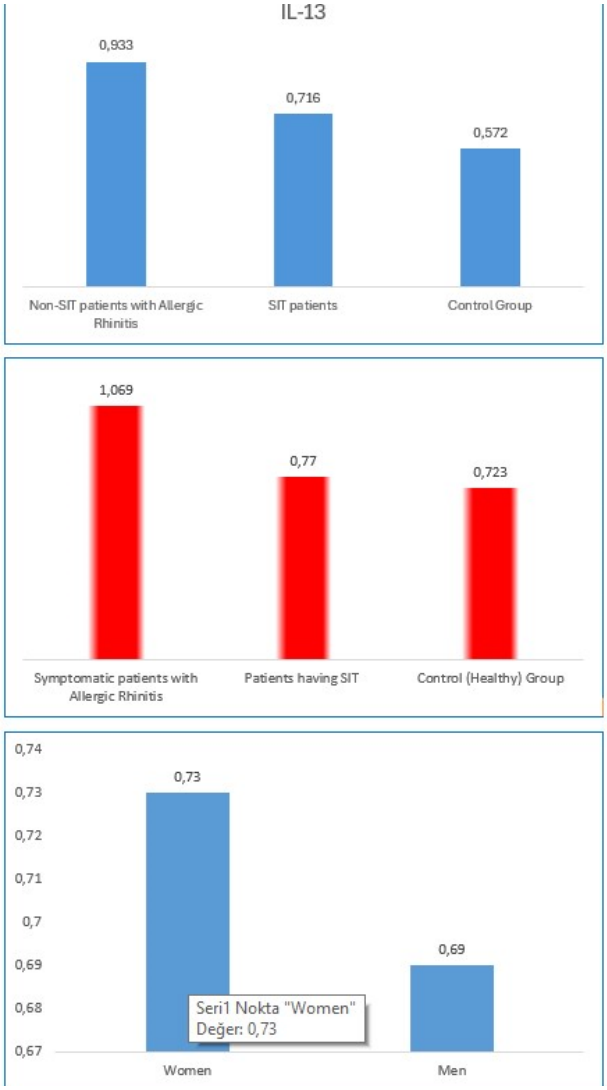

Figure 1

When the serum IL-13 and IL-8 levels were compared between men and women in the groups, no statistically significant differences were observed in Group 1 ($p>0.05$). In Group 2, IL-13 levels were significantly higher among women than men (0.73±0.04 pg/mL vs. 0.69±0.04 pg/mL; $p<0.009$) (Table 4) (Figure 1).

Table 4: Statistical comparison of serum IL-13 and IL-8 levels between males and females in the allergic rhinitis patient groups (Mann-Whitney U test)

	No SIT			SIT		
	Male (n=12)	Female (n=30)	p value	Male (n=14)	Female (n=28)	p value
IL-13 (pg/dL), mean ± SD	0.94 ± 0A5	1.01 ± 0.22	0.238	0.69 ± 0.04	0.73 ± 0.04	0.009
IL-8 (pg/dL), mean ± SD	1.02 ± 0.08	1.08 ± 0.13	0.058	0.76 ± 0.07	0.78 ± 0.07	0.486

SIT: Specific immunotherapy

Discussion

This study included 42 allergic rhinitis patients who were not receiving SIT and were symptomatic, 42 allergic rhinitis patients who were receiving SIT and were asymptomatic, and 23 healthy control subjects. The effect of both immunotherapy and sex on IL-13 and IL-8 levels was examined. There were statistically significant differences in IL-13 and IL-8 between symptomatic allergic rhinitis patients, those who had received SIT, and the control group. However, the only sex-based difference in cytokine levels was between the IL-13 levels of male and female patients who received SIT.

Pawankar et al. reported high levels of IL-13 in patients with allergic rhinitis. Similarly, in our study IL-13 levels were highest among patients with symptomatic allergic rhinitis.[9] We found that IL-13 levels were low in patients who received SIT, consistent with the study by Plewako et al. However, a study by Gogishvili et al. suggested that IL-13 inhibition did not play a major role in the treatment of allergic events. In our study, we observed that IL-13 levels tended to decrease in patients who received SIT.[10,11]

The molar structure of IL-8 is one of the most potent chemoattractants for neutrophils. At the same time, it stimulates the degranulation of polymorphonuclear lymphocytes and the binding of endothelial cells to CD11 and CD18. During the inflammatory response, IL-8 appears relatively later than other chemoattractants. While LTB4 concentration decreases, newly synthesized IL-8 begins to be secreted and exerts its effect for 24 hours. Among the chemokines, RANTES and IL-8 play important roles in eosinophil chemotaxis. Levels of RANTES and IL-8 in nasal lavage and bronchoalveolar lavage fluids were reported to increase after allergen exposure . Similarly, there was a significant difference in serum IL-8 levels between allergic rhinitis patients with and without SIT in our study.[12,13,14]

Lin Chuang et al. examined changes in IL-8 and TNF-alpha levels after SIT in seasonal and non-seasonal allergic rhinitis and found that levels of TNF-alpha and IL-8 were higher in the rhinitis groups than in healthy controls and decreased significantly in rhinitis patients after SIT.[15] In our study, we detected no significant difference between patients who received SIT and the healthy control group. This may be due to the classification of seasonal allergy.

Klein et al. showed that eosinophils concentrations were increased in tissue biopsy samples after nasal allergen exposure and that the cells expressed IL-8, IL-6, IL-13, IL-10, IL-4, and RANTES mRNA. The presence of cells carrying IL-10 and IL-13 mRNA was detected in tissue samples one week after nasal provocation . This supports our method of detecting the effectiveness of SIT in allergic rhinitis patients as a decrease in IL-13 level.[16]

In a study conducted by Kue-Hsiung et al., immunotherapy was administered to children diagnosed with allergic asthma, and analysis of beta chemokine, alpha chemokine, and IL-8 levels in the blood showed that among mite-sensitized patients, those who responded better to immunotherapy had lower beta chemokine and higher IL-8 levels.[17]

Both Rajakulasingam et al. and Klein et al. reported that levels of IL-8 increased after allergen exposure. Similarly, IL-8 levels in our study were highest among symptomatic allergic rhinitis patients. Our results support those of Lin Chuang et al., who reported that IL-8 levels were higher in patients with allergic rhinitis compared to the control group and lower in those receiving immunotherapy.

Numerous studies have demonstrated the efficacy and safety of SIT. The WHO and EAACI have reported that when given at sufficient concentrations, nasal and sublingual administration is as effective and reliable as injections.[18,19] This was confirmed by a 2000 meta-analysis of 54 clinical studies involving asthma patients.[20] In a study conducted by Reha et al., 56 patients receiving SIT and 51 patients receiving pharmacotherapy were examined for 5 years, and it was observed that 44 patients in the SIT group and 33 patients in the pharmacotherapy group were asymptomatic. SIT is shown to significantly reduce symptoms and prevent the development of new sensitization in allergic patients.[21]

In a study conducted by Pifferi et al., a portion of asthmatic patients were given SIT and compared with the untreated control group, and SIT was associated with a significant decrease in symptoms.[22] Waller et al. also showed that seasonal asthma symptoms decreased after SIT with meadow pollen extracts.[23] Dockic et al. examined allergic rhinitis patients receiving immunotherapy for 2 years and observed significant differences in nasal symptoms and skin prick test results between the placebo and study group.[24] Similarly, in the clinical evaluation of the patients in our study, allergic symptoms were nonexistent or mild in patients receiving SIT but ranged from moderate to severe in those not receiving SIT.

Studies in the literature evaluating the relationship between allergic rhinitis and gender reported that the prevalence of allergic rhinitis is higher in women. A retrospective study by Barlay et al. examining 3750 patients in our country also indicated that allergic rhinitis and rhinitis symptoms were more common in women. However, other studies in the literature reported that the frequency of allergic rhinitis is higher in men.[25]

In the present study, we observed no significant sex difference in IL-13 and IL-8 levels among patients not receiving immunotherapy, which supports the literature. Among the patients receiving immunotherapy, the IL-13 level was lower among male patients, while IL-8 levels were similar in male and female patients. Although the involvement of IL-13 and IL-8 in allergic rhinitis has been demonstrated, prospective randomized controlled studies with larger patient series are needed to elucidate the cause of these controversial conflicting results between the sexes. Recent studies have also indicated that immunotherapy not only reduces IL-13 and IL-8 levels but may also play a significant role in altering the Th1/Th2 balance, thereby enhancing the long-term management of allergic rhinitis.[26] This emphasizes the potential of SIT as an effective therapeutic option, further substantiating the findings of our study.

Immunotherapy has proven efficacy in preventing allergic events. Although the exact mechanism of action is not known, changes in cytokine levels are believed to play an important role. Cytokines have a major role in the physiopathology of allergic rhinitis. Of these, eosinophil cationic protein, IL-5, tryptase, IL-4, IL-13, and IL-8 are several important mediators. In our study, IL-8 and IL-13 levels were measured in patients with symptomatic allergic rhinitis, in a group of patients receiving SIT, and in a healthy control group. IL-13 and IL-8 levels were lower in patients receiving immunotherapy, supporting the literature data discussed above. IL-8 and IL-13 are two important mediators involved in allergic rhinitis, and their suppression is one of the mechanisms of action of immunotherapy. However, further studies are needed to investigate the specific roles of IL-13 and IL-8 inhibition in treatment.

Conclusion

The results of this study show that serum IL-13 and IL-8 levels in patients with allergic rhinitis tended to decrease significantly after immunotherapy. When compared according to sex, only IL-13 level differed significantly between men and women receiving immunotherapy.

References

1. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. Allergy. 2005;60:350.
2. Bozkurt B, Karakaya G, Kalyoncu AF. Seasonal rhinitis, clinical characteristîcs and risk factors for asthma. Int Arch Allergy Immunol. 2005;138:73-79.
3. Cecil Textbook of Medicine Cilt 2 2006 s(1605-1610).
4. İliçin, Biberoğlu, Süleymanlar, Ünal İç Hastalıkları 2003 Cilt 2 s(2586-2592)
5. Karakaya G. Rinit Epidemiyolojisi. Türkiye Klinikleri J-Allergy-Astma 2002 4:(14-18)
6. Allergy Cytokines in Allergic Inflammation Larry Borish and Lanny J.Rosenwasser Chapter 10 s(108-123)
7. Grammer LC, Greenberger PA. Allergic rhinitis, Patterson's Allergic Disease'(Grammer LC)'den. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2002 s. 159-182
8. Skoner DP. Allergic rhinitis:Defînition,epidemology,patophysology, detection and diagnosis. J Allergy Clin Immunol.2001:108:s2-8
9. Pawankar RU, Okuda M, Hasegawa S,Suzuki K, Yssel H, Okubo K,et al. IL-13 expression in the nasal mucosa of perennial allergic rhinitis. Am J Respir Crit CareMed 1995;152:2059-67
10. Tea Gogishvilli, Christian Hahni Julia Meinhard et al. înhibition of IL-4/IL-13 does not enhance the efficacy of allergen immunoterapy in murin allergic airway inflammation Int Arch Allergy Immunol 2007;142:165-174
11. Halina Plewako, Katarzyna Wosinska, Monica Arvidsson et al. Basophil IL-4 and IL-13 production is supressed during the early phase of rush immunoterapy Int Arch Allergy Immunol 2006;141:346-353
12. Rajakulasingam K,Hamid Q,0'Brien F, Shotman E, Jose PJ, Williams TJ, Et al. RANTES in human allergen induced rhinitis:cellular source and relation to tissue eosinophilia. Am J Respir Crit Care Med 1997;155:696-703
13. Tworek D, Bochehska-Marciniak M, Kupczyk M, Görski P, Kuna P. The effect of 4 weeks treatment with desloratadine (5mg daily) on levels of interleukin (IL)-4, IL-10, IL-18 and TGF beta in patients suffering from seasonal allergic rhinitis Pulm Pharmacol Ther. 2007;20(3):244-9. Epub 2006 Mar 10
14. Dougles JA, Dhami D, Gurr CE, Bulpitt M, Shute JK, Howarth PH, Et al Influence of IL-8 challenge in the nasal mucosa in atopic and non atopic subjects. Am J Respir Crit Care Med 1994,150:1108-13
15. Lin Chuang Er Bi Yan Hou Ke Za Zhi The effect ofTNF alpha and IL-8 in the pathogenesis of allergic rhinitis.2006 Dec;20(23): 1060-1
16. KleinJan A, Dijkstra MD, Boks SS, Severijnen LA, Mulder PG, Fokkens WJ Increase in IL-8, IL-10, IL-13, and RANTES mRNA levels (in situ hybridization) in the nasal mucosa after nasal allergen provocation J Allergy Clin Immunol. 1999 Mar; 103(3 Pt l):441-50.
17. KueHsiung Hsieh,MD,Chen C. Chou,MD, Immnoterapy supressed the production of monocyte chemotactic anda activating factor and augments the production of IL-8 in children asthma 1995 Dec.15Tahami RV, Çorakçıoğlu S,Sonkaya G:Flutikazon Propionatın Perennial Alleıjik Rinitli Hastalarda Klinik Etkinliği, ekimler Yaym Birliği KBB, 1995:1:27-31
18. EAACI. Immunoterapy.Position paper. Allergy. 1988;43:1-33
19. Bousquet j,Lockey R,Mailing HJ.A Allergen Immunoterapy:therapeutic vaccines for allergic diseases. A WHO position paper.. J Allergy Clin Immunol.l 998; 102(4 Pt l):558-62
20. Abramson MJ., Puy RM,Weiner JM. Allergen Immunoterapy for asthma. Cochrane database Syst Rev 2003;(4):CD001186
21. CM Reha, A Ebru. Specific immunoterapy is effective in the prevention of new sensitivities. Allergologia et immunopatologia. March 2007. Volume 35- number 02 p.44-51
22. Pifferi M, Baidini G, Marazzını G et al. Benefîts of immunoterapy with a standardized Dermatophagoides pteronyssinus extract in asthmatic children: a three year prospective study. Allergy.2002;57:785-90
23. Walker SM. Grass pollen immunoterapy for seasonal rhinitis and asthma: a randomized, controlled trıal. J Allergy Immunol. 2001;107:87-93
24. Dockid D,Schnitker J,Narkus A. Clinical effects of spesıfic immunoterapy: A two year double-blind, placebo-controlled study with a one year follow up. Clinic of Pulmonology and AUergology,2005 Dec; 26(2):113-2
25. Dr. Fevzi Barlay Prof. Dr. Bülent Topuz Denizli ili ve çevresindeki alerjik rinit ön tanılı olgularda deri prick testi sonuçlarımız; 15 yıllık retrospektif çalışma uzmanlık tezi Denizli – 2019
26. Wang, J., Zhou, Y., Zhang, H. et al. Pathogenesis of allergic diseases and implications for therapeutic interventions. Sig Transduct Target Ther 2023;8(138).

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CASE REPORT

Navigating Rhupus Complexity

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Abstract

The term 'Rhupus,' introduced by Peter Schur in 1971, describes patients meeting criteria for both rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Rhupus (RhS) is a rare syndrome, and approximately 60 cases have been described in the literature to date. The challenges in diagnosing this disease stem from the lack of well-defined clinical criteria. In this case, we present a 42-year-old female patient with overlap syndrome of RA and SLE (RhS) who developed inflammatory arthritis, swelling in her bilateral wrists, severe malar rash, oral ulcers and alopecia, anemia and thrombocytopenia during follow-up. Upon arrival, the patient's laboratory values were as follows: erythrocyte sedimentation rate: 61 mm/hour (normal value: 0-20), hemoglobin: 8.3 g/dL (12-16), platelet count: 112.103/µL (150-450.103/µL). The purpose of documenting this case is to share our own experience with a syndrome that is quite rare and has the potential to cause confusion in the daily practice of clinicians.

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Introduction

Autoimmunity is one of the top ten causes of mortality and morbidity in young women, occurring at similar rates in different parts of the world. Approximately 20% of patients with a history of autoimmunity may develop additional autoimmune diseases, leading to overlapping conditions.[1] The term 'Rhupus,' introduced by Peter Schur in 1971, describes patients meeting criteria for both rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[2] Rhupus (RhS) is a rare syndrome, and approximately 60 cases have been described in the literature to date. The challenges in diagnosing this disease stem from the absence of well-defined clinical criteria.[3] Generally, Rhupus is known for having less internal organ involvement than SLE. It is a neglected topic that arises concurrently with the development of RA and SLE, respectively. It is estimated that the Rhupus syndrome develops in 0.05% to 2% of patients with RA or SLE.[4] Although the cause of this disease has not been fully elucidated, the literature suggests that various genetic, environmental and immunological factors may play a role.[1]

Some authors have described Rhupus syndrome as a subtype of SLE accompanied by severe arthritis. In the course of lupus, three types of joint involvement can be observed: non-erosive arthropathy (the most common, known as Jaccoud), erosive symmetric polyarthritis (Rhupus syndrome), and mild deforming arthropathy.[5] However, the widely accepted perspective is that this involves deforming, symmetrical, erosive polyarthritis accompanied by the symptoms and signs of SLE. It is characterized by the presence of specific antibodies crucial for diagnosis, including Anti-Smith (anti-Sm), Anti-double stranded DNA (anti-ds DNA), and anti-cyclic citrullinated peptide (anti-CCP).[6]

Case

In this case, we present a 42-year-old female patient with overlap syndrome of RA and SLE (RhS) who developed anemia and thrombocytopenia during follow-up. The purpose of documenting this case is to share our own experience with a syndrome that is quite rare and has the potential to cause confusion in the daily practice of clinicians. A 42-year-old female patient has been under our rheumatology outpatient clinic's follow-up since 2019, diagnosed with seropositive rheumatoid arthritis. The diagnosis was supported by clinical evidence of inflammatory arthritis, along with positivity for rheumatoid factor (RF) and anti-CCP (> 500 IU/ml). The patient met the 2010 classification criteria for RA with a score of 8, established by the American College of Rheumatology/European League Against Rheumatology (ACR/EULAR).[7] Until 2022, there was no history of treatment other than oral methotrexate 15 mg per week, which had clinically controlled her disease. Apart from the diagnosis of RA, she had no comorbidities, family history of autoimmune disease or smoking history. In 2022, the patient applied to the rheumatology clinic with complaints of red rashes on the cheeks, sores in the mouth, hair loss, fever and increased joint pain. Physical examination revealed severe malar rash, oral ulcers, and alopecia, with swelling in the bilateral metacarpophalangeal joints and wrists. (Figure 1 and Figure 2). Hand radiographs revealed periarticular osteoporosis and narrowings between the joints (Figure 3) The patient's vitals showed a temperature of 37.8°C. There was no evidence of hypotension or tachycardia. In the application laboratory, Antinuclear antibody was positive at 1/160 dilution and had a homogeneous pattern. Anti-Sm and anti-ds-DNA positivity was detected in the patient's extractable nuclear antigen profile (ENA). The patient had hypocomplementemia in serological profile, with C3 level of 0.75 g/L (normal value: 0.9 - 1.8) and C4 level of 0.11g/L (normal value: 0.1 - 0.4). As a result of the evaluations, the patient was diagnosed with SLE according to the ACR/EULAR 2019 classification criteria with a score of 33.[8] Since she also had seropositive RA, we were following up with the diagnosis of Rhupus syndrome. In other laboratory findings: creatinine: 0.9 mg/dL (normal value: 0.7-1.20 mg/dL), C- reactive protein (CRP): 32 mg/L (normal value: 0-5 mg/dL), erythrocyte sedimentation rate: 61 mm/hour (normal value: 0-20 mm/hour), hemoglobin: 8.3 g/dL (normal value: 12-16 g/dL), platelet count: 112.103/µL (normal value: 150-450.103/µL) were detected. This anemia and thrombocytopenia were thought to be autoimmune. Coombs tests were positive, and the peripheral blood smear revealed no schistocytes, with thrombocytes appearing normal. Transferrin saturation was 30%, ferritin was 29 ng/ml (normal range: 13-150 ng/ml), mean cell volume was 86 femtoliters (normal range: 80-100), folate was 8 ng/ml (normal range: 2.7-17), and vitamin B12 was 300 pg/ml (normal range: 160-950). Considering the clinical condition and laboratory parameters, hydroxychloroquine 200 mg twice

a day and methylprednisolone (24 mg) were added to the patient's treatment. The steroid dose was gradually reduced to 8 mg/day. After a two-month follow-up, significant improvement was observed in the patient's clinical condition, including a reduction in mouth sores, hair loss, and joint symptoms and swellings. In the blood taken during this follow-up, CRP: 16 mg/L, platelet count: 132.103/µL, and hemoglobin: 9.3 g/dL were detected. Going forward, the plan is to further reduce the steroid dose to 5 mg/day based on the clinical situation, introduce mycophenolate mofetil to the treatment in combination with methotrexate.

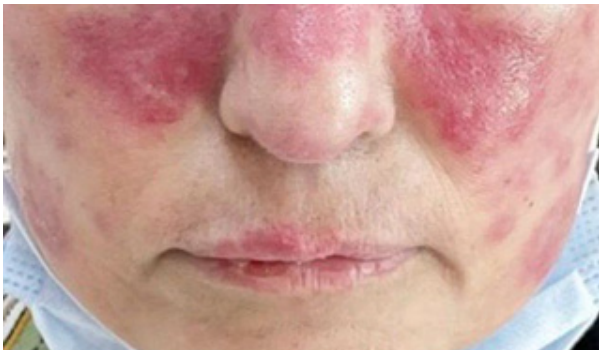

Figure 1: Severe malar rash of our patient

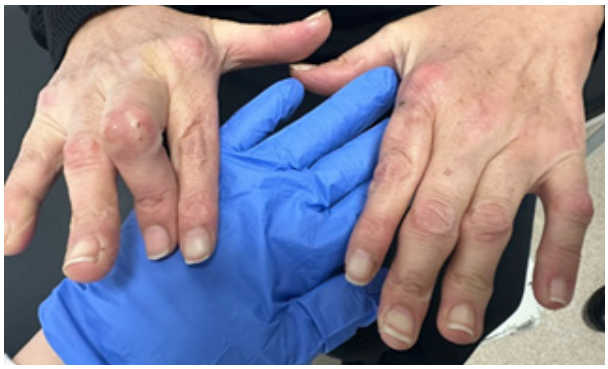

Figure 2: Swelling in metacarpophalangeal joints and wrists, hand deformities

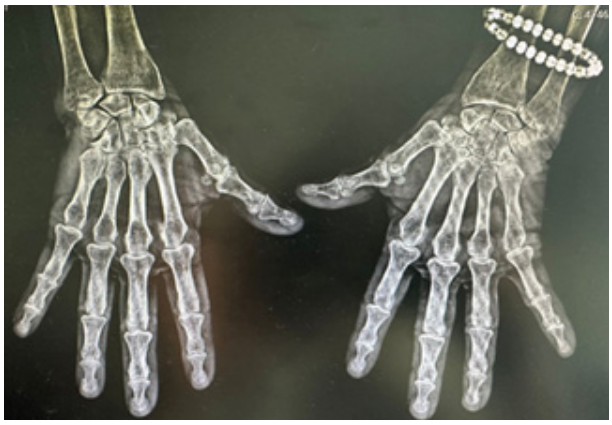

Figure 3: Hand X-ray

Discussion

The diagnosis of Rhupus syndrome can be quite challenging due to the absence of specific classification criteria.[9] Previous case series have suggested that Rhupus should be considered in patients with SLE symptoms who also present with anti-CCP positivity and elevated CRP levels, a condition generally observed in women.[10]

In our case, the diagnosis was supported by the presence of chronic symmetric polyarthritis, malar rash, alopecia, mucosal involvement, and hematological manifestations, all of which developed in the course of SLE. Although skin biopsy is not deemed essential for diagnosis according to the literature, it can be helpful in ruling out other erythematous diseases.[11] However, we opted not to perform a skin biopsy due to the involvement of multiple systems and the simultaneous presence of anti-Smith, anti-CCP, and anti-dsDNA antibodies. While some rheumatologists may categorize RhS as a subtype of SLE, the coexistence of anti-Smith and anti-CCP antibodies alongside ANA and RF positivity in our patient suggests that RhS is more appropriately characterized as an overlap syndrome rather than a distinct type of SLE.[12] Furthermore, the elevated levels of anti-CCP and CRP observed in our patient align with the serological profile typically associated with RhS.

The literature suggests that, in the majority of cases, the diagnosis of RA precedes the diagnosis of SLE by several years, with SLE developing within four to seven years after the initial RA diagnosis.[10] In accordance with this pattern, in our case, RA manifested three years before the diagnosis of SLE. It is noteworthy that renal and neurological involvement is less frequently observed in RhS compared to SLE patients without a prior RA diagnosis. For instance, glomerulonephritis and serositis appear to be rare in comparison to SLE cases.[13] High disease activity in SLE, the use of high steroid doses during induction, or the necessity for pulse steroid therapy are less common in Rhupus patients. Similarly, in our case, we observed improvement in both clinical and laboratory parameters before the need for pulse steroids arose.

Genetic studies are also highlighted in the literature as a diagnostic tool for the disease. It has been recognized that genes such as programmed cell death 1 (PDCD1), signal transducers and activators of transcription 4 (STAT4), and protein tyrosine phosphatase nonreceptor 22 (PTPN22) are associated with RA and SLE. Additionally, some studies indicate that hu-

man leukocyte antigen (HLA) DR1 and DR2 alleles are more prevalent in Rhupus syndrome.[14] However, due to the financial conditions of our country, genetic testing was not conducted on our patient.

Symmetrical and bilateral erosive joint damage was evident in the physical examination and hand radiograph of our patient. The symmetric bilateral erosive arthritis pattern aligns with one of the 2020 EULAR/ACR classification criteria for RA. Additionally, according to research by Chan et al., SLE patients who test positive for anti-CCP are more prone to develop erosive arthritis.[15] There is a belief that anti-CCP may play a pathogenic role in erosions. Consistent with this, erosive arthritis was observed in our patient.

There is limited information available on the treatment of RhS, and the existing data are primarily derived from a small number of case studies and series. Treatment regimens typically involve low-to-moderate doses of corticosteroids combined with multiple disease modifying anti rheumatic drugs (DMARDs, such as methotrexate) in Rhupus patients with significant joint involvement to prevent the progression of erosive arthritis.[16] We also implemented this treatment for our patient. But in some studies have indicated that DMARDs alone may not be adequate for managing RhS.[5] Mycophenolate mofetil and cyclosporine have both proven effective in treating RhS.[10,17] In contrast, anti-TNF therapies have shown minimal benefits for Rhupus or SLE and, despite their success in RA, have been reported to exacerbate RhS in some cases.[9] However, if internal organ involvement develops or if there is clinical deterioration, options such as mycophenolate mofetil, other biological treatments, rituximab, and abatacept may be considered.[18,19] In our case despite concurrent thrombocytopenia and anemia, a positive response to the treatment was achieved without the need for mycophenolate mofetil.

This case outlines the presentation of a 42-year-old woman with erosive arthritis accompanied by mucosal findings, diagnosed and followed as Rhupus syndrome. Our patient showed a positive response to the treatment involving steroids and hydroxychloroquine. To the best of our knowledge, this represents the tenth reported case of adult Rhupus syndrome in our country. Additionally, we aimed to enhance awareness among RA patients regarding the potential co-occurrence of SLE in the course of their condition. Approaching it from this perspective may prove beneficial, particularly for young female RA patients.

References

1. Alfadhli S, Nizam R. Rhupus: A crosswalk between lupus and rheumatoid arthritis. OA Arthritis. 2014;10:2.
2. Schur P. Cecil-loeb textbook of medicine. 1971.
3. Simón JA, Granados J, Cabiedes J, Morales JR, Varela JA. Clinical and immunogenetic characterization of Mexican patients with 'rhupus'. Lupus. 2002;11(5):287-92.
4. Solis Cartas U, Martínez Larrarte JP, Prada Hernández DM, Gómez Morejón JA, Valdés González JL, Molinero Rodríguez C. Rhupus syndrome. A rare combination. Revista Colombiana de Reumatología. 2017;24(4):237-41.
5. Pipili C, Sfritzeri A, Cholongitas E. Deforming arthropathy in systemic lupus erythematosus. Eur J Intern Med. 2008;19(7):482-7.
6. Agha RA, Franchi T, Sohrabi C, Mathew G, Kerwan A, Thoma A, et al. The SCARE 2020 guideline: updating consensus surgical CAse REport (SCARE) guidelines. International Journal of Surgery. 2020;84:226-30.
7. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-81.
8. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Annals of the Rheumatic Diseases. 2019;78(9):1151-9.
9. Iaccarino L, Gatto M, Bettio S, Caso F, Rampudda M, Zen M, et al. Overlap connective tissue disease syndromes. Autoimmun Rev. 2013;12(3):363-73.
10. Benavente EP, Paira SO. [Rhupus: report of 4 cases]. Reumatol Clin. 2011;7(5):333-5.
11. Ziaee V, Moradinejad MH, Bayat R. RHUPUS Syndrome in Children: A Case Series and Literature Review. Case Rep Rheumatol. 2013;2013:819629.
12. Pichilingue GS, Campos JG, Zevallos JC. Características clínicas y hallazgos histopatológicos de glomerulonefritis lúpica en pacientes con Rhupus en el Hospital Nacional Arzobispo Loayza en los años 2003 al 2009. Acta Médica Peruana. 2011;28(2):79-81.

13. Shovman O, Langevitz P, Shoenfeld Y. Rhupus; unusual presentations. Clin Rheumatol. 2015;34(12):2041-6.
14. Orozco G, Eyre S, Hinks A, Bowes J, Morgan AW, Wilson AG, et al. Study of the common genetic background for rheumatoid arthritis and systemic lupus erythematosus. Ann Rheum Dis. 2011;70(3):463-8.
15. Chan MT, Owen P, Dunphy J, Cox B, Carmichael C, Korendowych E, McHugh NJ. Associations of erosive arthritis with anti-cyclic citrullinated peptide antibodies and MHC Class II alleles in systemic lupus erythematosus. The Journal of Rheumatology. 2008;35(1):77-83.
16. Tani C, D'aniello D, Delle Sedie A, Carli L, Cagnoni M, Possemato N, et al. Rhupus syndrome: assessment of its prevalence and its clinical and instrumental characteristics in a prospective cohort of 103 SLE patients. Autoimmunity reviews. 2013;12(4):537-41.
17. Seo SR, Lee SJ, Park DJ, Kim TJ, Park YW, Lee SS. Successful treatment using cyclosporine in a patient with rhupus complicated by aplastic anemia: a case report and review of the literature. Clin Exp Rheumatol. 2011;29(4):708-11.
18. Andrade-Ortega L, Irazoque-Palazuelos F, Muñóz-López S, Rosales-Don Pablo VM. Efficacy and tolerability of rituximab in patients with rhupus. Reumatol Clin. 2013;9(4):201-5.
19. Pinto LF, Velásquez CJ, Prieto C, Mestra L, Forero E, Márquez JD. Rituximab induces a rapid and sustained remission in Colombian patients with severe and refractory systemic lupus erythematosus. Lupus. 2011;20(11):1219-26.