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Gallstones at chronic spontaneous urticaria patients: A retrospective clinical study

Assoc. Prof. Dr. Arzu Ataseven¹, Res. Asst. Koray Durmaz¹, Asst. Prof. Dr. Ilkay Ozer¹, Prof. Dr. Recep Dursun¹

¹Necmettin Erbakan University, Meram Medicine Faculty, Department of Dermatology, Konya, TURKEY

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Corresponding author: Assoc. Prof. Dr. Arzu AtasevenMD.

Necmettin Erbakan University, Meram Medicine Faculty, Department of Dermatology, Konya/Turkey

+903322236391/ arzuataseven@hotmail.com

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INTRODUCTION

Chronic urticaria is a skin disease characterized by spontaneously appearing itchy wheals anywhere on the body lasting for more than 6 weeks. It can be accompanied by angioedema, life-threatening condition because of swelling in the deep layers of the skin and subcutaneous tissues. Chronic urticaria is categorized by whether it is inducible or not. If autoantibodies or unknown causes induce the disease, it is called chronic spontaneous urticaria (CSU).¹ The inflammation role in the CSU pathogenesis is still debated. In this study, we would like to investigate the possible relationship between the gallstones, inflammation markers and CSU in CSU patients.

MATERIALS and METHODS

Clinical Data

We selected patients with diagnoses of CSU recruited from dermatology outpatient clinics and the files of patients were scanned retrospectively between Sep2017-Sep2019. The patients were referred to the clinic with wheals lasting for less than 24 hours without angioedema. The above 18 years of age were determined as the inclusion criteria for the study. The patients tested for CBC, CRP, ALT, AST, GGT, ALP, total bilirubin, direct bilirubin by a blood sample and transabdominal ultrasound (TUS) for etiology were included in the study. Neutrophil/Lymphocytes Ratio (NLR) and Platelets/Lymphocytes Ratio (PLR) were calculated from CBC. The necessary approval was obtained from the ethics committee of Necmettin Erbakan University.

Data Acquisition and Assessments

The patients' demographic data, body-mass index (BMI), duration of the CSU, history of the drugs for CSU, additional systemic diseases and drug history for these, pregnancy state, history of hormone replacement therapy or oral contraceptives, history of rapid weight loss, history of family, accompanying abdominal symptoms, blood tests results, TUS results for accompanying choledocholithiasis or cholelithiasis were collected from files of the patient. BMI was classified as underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$), normal weight ($\text{BMI} 18.5$ to 25 kg/m^2), overweight ($\text{BMI} 25$ to 30 kg/m^2) and obese ($\text{BMI} > 30,0 \text{ kg/m}^2$) adopted by the National Heart, Lung, and Blood Institute in 1998.²

Statistical Evaluation

All statistical analyses were carried out using IBM SPSS software version 22. The relation between independent categoric variables was performed using the crosstabs function of descriptive statistics. The data were summarized with the number, percentage, mean (min-max.) which are appropriate to the distribution. The relation between numeric values and independent categoric values was performed using the independent samples T-test function. In the analysis, p-values < 0.05 were considered statistically significant.

RESULTS

108 patients with CSU (32 males and 76 females), aged 18 to 82 years (mean age, 41.78 ± 14.44 years) were included in the study. The patients' BMI values and groups were calculated. There was not any person in the underweight class ($\text{BMI} < 18.5$). 20 patients had cholecystectomy history ($n=11$) or gallstone finding in the TUS (choledocholithiasis or

cholelithiasis) (n=9) and named as group A. 88 patients had no history of cholecystectomy or gallstone finding in the TUS and named as group B (table I). The duration of the CSU disease significantly differed between of the groups. It was longer in group A ($7,36 \pm 5,66$) than group B ($4,52 \pm 4,81$) ($p < 0,05$). There was no pregnant in the study. We detected 4 patients (3.7%) had no history of antihistamines for CSU. 25 patients (23.1%) had just used antihistamines for relief. Omalizumab and other drugs for urticaria (cyclosporine, montelukast, etc.) were used combined by 49 patients (45.3%) for the controlling symptoms in CSU. We observed there were no significant abdominal symptoms (pain on the right upper quadrant, epigastrium, right shoulder, etc.). difference between groups. 53 patients (59.1%) had additional systemic disease. The most observed comorbidity was hypertension in 14 patients (12.9%). 65 patients (%60.2) had drug use history for systemic diseases. We observed WBC count is $9,38 \pm 2,37$ in group A and $8,03 \pm 2,04$ in group B. This difference was significant statistically ($p < 0,05$). Platelet count was also differ between two groups significantly (group A = $328,70 \pm 85,62 \times 10^3/\text{mm}^3$ vs group B = $287,12 \pm 72,77 \times 10^3/\text{mm}^3$) ($p < 0,05$). Neutrophil count was more in group A ($5,87 \pm 1,65$) than group B ($4,76 \pm 1,75$) ($p < 0,05$). NLR and PLR values did not differ significantly between the two groups (Table II). When we looked at the serum biochemistry panel (CRP, ALT, AST, GGT, ALP, Total bilirubin, direct bilirubin), there is no difference between the two groups significantly (Table III). The history of hormone replacement therapy (HRT) or oral contraceptives (OCPs) in group A and group B was no differ significantly ($p > 0,05$). Rapid weight loss history of the patients also not differed between group A and group B patients significantly ($p > 0,05$). The gallstone history of the family was significantly higher in group A (n=12 positive/8 negative) than group B (n=26 positive /62 negative)

($p < 0.05$). In the family history positive group ($n=38$), the most presented relative was mothers ($n=21$).

DISCUSSION

In this study, we aimed to find a possible relations between gallstones and CSU mainly. We observed WBC, neutrophils count and platelet count were significantly different in group A than group B. Gallstones are pigmented cholesterol stones and formed mostly of cholesterol. When bile becomes supersaturated due to unproportional concentrations, the excess cholesterol precipitates as monohydrate crystals. Firstly, these crystals cause biliary sludge by embedding in the gallbladder mucin gel with bilirubinate. Then, this process eventuates gallstone formation by aggregating the sludge.³ Risk factors for gallstone formation include genetic predisposition and environmental factors. An inflammatory process can also play a role in stone formation. Common clinical findings are pain on the right upper quadrant of the abdomen, fever and jaundice in biliary diseases, but asymptomatic bile duct stones can be possible.⁴ Blood tests and TUS are the most commonly used initial tests for diagnosis biliary stones. Abnormal liver function tests, serum alkaline phosphatase and gamma-glutamyl transpeptidase levels are generally detected increased in symptomatic patients. TUS has a very high specificity in the detection of bile stones even if it has a low sensitivity (25-60%).^{5,6} Bile duct stones can also be a trigger in the inflammation process according to the cause of acute cholangitis.⁷ In our knowledge, there are no such studies investigate of the relation between CSU and gallstones. In an article from UK⁸, this association was discussed. B.Dharmagunawardena et al., reported a case of chronic urticaria in a patient who had a gall stone in the common bile duct. In this case, the 63-year-old woman

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patient who had a 3month history of recurrent urticaria had also suffered from a pain in the right hypochondrium and shoulder. She had experienced cholecystectomy 18 years ago and these symptoms were also accompanied the urticaria episodes at that time. At this time there was no abnormality detected in CBC and serum biochemistry values. TUS revealed a dilated common bile duct with a gall stone at the lower end and the gallstone was removed at the endoscopic retrograde cholangiopancreatogram (ERCP) session. Her urticaria symptoms improved dramatically and after more than 2 years to date, she had not experienced urticarial episodes. In this case report, authors draw attention to the stone may well have been the provoking factor in the urticarial episodes and they suggested this possible association should be considered in the patients have appropriate symptoms.

Certain etiology of CSU is still not elucidated even if, some autoimmune cases have been proposed.⁹In the literature, an interplay between CSU and inflammation has been reported as a pathomechanism.¹⁰ The inflammation role in the CSU pathogenesis is supported by the correlation between C-reactive protein (CRP) (a well known acute phase reactant) and matrix metalloproteinases-9 (MMP-9) levels and disease activity. In our study, we could observe CRP level in 85 patients. It did not differ between group A and group B(table III). Evidence of an inflammatory response in CSU was also supported by the activation of dermal mast cells and secreted mediators such as histamine, proteases, tumor necrosis factor- α (TNF- α) and interleukin-1 (IL-1). Inflammation has been associated with disease severity and disease activity within patients.¹¹In recent studies,the ratio of neutrophil to lymphocyte (NLR) and the ratio of platelet to lymphocyte (PLR) which are inflammatory parameters have been used as markers in many chronic diseases such as familial mediterranean fever, psoriasis and

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rheumatoid arthritis. These markers were studied on 106 CSU patients in a retrospective study from Turkey.¹²In this study, CBC, CRP levels were measured before omalizumab treatment and at the third months of treatment were compared. NLR and PLR values were also calculated from CBC. At the result of three months, there was a significant decrease in WBC, PLT, neutrophils, CRP level, NLR and PLR however a significant increase in MPV and eosinophils. R.Medha et al.¹³ measured inflammatory markers (plasma IL-6 and CRP) levels in 45 CSU patients and obtained data were compared with healthy controls' results. In patients with CSU, IL-6 and CRP levels were detected elevated and these markers were also correlated with severity scores in CSU patients. In another study from Poland¹⁴, MPV, PDW, platelet count and CRP levels were measured in CSU patients and compared with healthy controls. While the platelet count and CRP levels were significantly higher in CSU patients than healthy ones. They were also correlated with the severity of the disease. There were no significant differences were detected in PDW and MPV values between CSU patients and healthy controls. In our study, WBC, neutrophil counts and platelet counts were observed higher in group A than group B significantly. CRP, NLR and PLR values did not differ significantly between the two groups.

CONCLUSION

In this study, we investigated the possible relation between CSU, inflammation and gallstones. We would like to underline as a limitation, this was a retrospective study and CRP,

GGT values of the some patients were missed. It is needed to perform further investigations, with larger groups of patients in order to assess the relationship between CSU and gallstones.

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Table I: Demographic data of the study groups

Study groups	Age	Sex		Weight class			p-value ^a	p-value ^b	p-value ^c
		Male	Female	NW	OW	O			
A (n=20)	44,15 (±12,79)	2 (10)	18 (90)	5 (25)	7 (35)	8 (40)	0,417	0,033*	0,229
B (n=88)	41,24 (±14,77)	30 (34,1)	58 (65,9)	29 (33)	40 (45,5)	19 (21,6)			
Total (n=108)	41,78±14,44	32 (29,6)	76 (70,4)	34 (31,5)	47 (43,5)	27 (25)			

Data are presented as mean ± standard deviation or frequency (%)

^aAge of group A vs age of group B

^bSex of group A vs sex of group B

^cWeight class of group A vs weight class of group B

*p<0,05 is considered statistically significant.

NW=Normal weight, OW=Overweight, O=Obese

Table II: Complete blood tests (CBC) results

		Group A (n=20)	Group B (n=88)	Cut-off value ^a	p value ^b
Complete blood count (CBC)	wbc (x10 ³ /mm ³)	9,38±2,37	8,03±2,04	4-10	0,011*
	mch	26,93±3,26	27,87±1,87	27,6-33,3	0,225
	rdw	14,10±1,70	13,71±1,26	10,5-15,5	0,257
	rbc (x10 ⁶ /mm ³)	4,96±0,47	4,97±0,42	3,6-5,7	0,912
	plt(x10 ³ /mm ³)	328,70±85,62	287,12±72,77	150-400	0,028*
	plr	135,64±42,33	126,32±56,52		0,490
	pdw	13,77±2,54	12,82±2,82	0-99,9	0,174
	neu(x10 ³ /mm ³)	5,87±1,65	4,76±1,75	1,5-7,3	0,011*
	nlr	2,42±0,87	2,13±1,25		0,333
	ly(x10 ³ /mm ³)	2,64±0,98	2,47±0,74	0,8-5,5	0,384
	eos(x10 ³ /mm ³)	0,16±0,10	0,15±0,11	0,2-0,6	0,639
	bas(x10 ³ /mm ³)	0,47±0,04	0,04±0,04	0-0,2	0,720
	mpv	9,88±1,54	10,01±1,22	7,8-11	0,684
	hb	13,28±1,71	13,84±1,41	12,1-17,2	0,125
	hct	40,07±4,12	41,27±3,69	36,1-50,3	0,202
	mo	0,65±0,23	0,59±0,21	0,2-0,9	0,258
	mcv	81,26±8,39	83,12±4,52	82,2-99	0,347
	mchc	33,08±1,25	33,52±1,14	32-36	0,123

Data are presented as mean ± standard deviation

^aCut-off value was described by the cut-off values of our clinic's laboratory

^bCell counts and other values in group A vs group B

*p<0,05 is considered statistically significant.

Table III: Serum biochemistry panel results

		Group A (n=20)	Group B (n=88)	Cut-off value^a	p value^b
Serum biochemistry panel	CRP*	3,36±3,77 (n=14)	8,05±13,64 (n=71)	0-5	0,207
	ALT (SGPT)	18,15±5,48	18,42±9,06	0-32	0,898
	AST (SGOT)	15,65±3,68	17,02±4,31	0-33	0,191
	GGT*	19,32±8,15 (n=19)	20,15±8,88(n=86)	0-40	0,708
	ALP	70,45±25,06	72,73±22,5	35-104	0,690
	Total Bil.	0,59±0,38	0,66±0,29	0,2-1,2	0,356
	Direct Bil.	0,22±0,10	0,24±0,09	0-0,30	0,425

Data are presented as mean ± standard deviation

^aCut-off value was described by the cut-off values of our clinic's laboratory

^bCell counts and other values in group A vs group B

*Missing value

p<0,05 is considered statistically significant.