Original Article

Monocyte-To-Lymphocyte Ratio May Be a Clue to Understand Underlying Cause of Pruritus in Chronic Kidney Disease

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Abstract

Aim: Pruritus is one of the most common dermatologic conditions in chronic kidney disease (CKD) patients. Uremic toxins, inflammation, imbalance in mineral metabolism, and altered hormonal status may constitute underlying causes. The present study aims to evaluate the association between inflammatory markers and pruritus, with or without the presence of xerosis, in CKD.

Materials and Methods: This observational and cross-sectional study compared CKD patients with pruritus and xerosis with CKD patients without pruritus and xerosis regarding inflammatory markers. Peripheral blood-derived inflammatory markers such as neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio were analyzed.

Results: A total of 92 patients were included in the study, 47 (51.1%) of whom had xerosis and/or pruritus. Pruritus and xerosis were significantly associated ($P < 0.001$), but there were also CKD patients with pruritus and without xerosis (28%). MLR was significantly higher in patients with pruritus, and in patients with both xerosis and pruritus, than in those without ($P = 0.037$ and $P = 0.046$, respectively). Dialysis status was not associated with pruritus ($P = 0.911$), and CRP levels in patients with dialysis were higher than those who did not receive dialysis ($P = 0.046$).

Conclusion: Higher MLR in patients with CKD-associated pruritus may suggest a role for monocytes in the mechanism of pruritus, where low-grade inflammation of CKD is an underlying cause. In the future, therapeutic measures to reduce monocyte activity may be studied to treat CKD-associated pruritus.

Keywords: Chronic kidney disease, inflammation, monocyte-to-lymphocyte ratio, pruritus

Introduction

Kidneys play a vital role in maintaining several critical physiological processes in the body, with both exocrine and endocrine functions. Exocrine functions include regulating fluid and electrolyte balance, acid-base equilibrium, and the removal of metabolic waste products, while endocrine functions involve activating vitamin D for calcium balance, blood pressure regulation, and erythropoiesis through hormone production.[1]

Chronic kidney disease (CKD) affects approximately 861 million people worldwide, with the majority suffering from the disease in its progressive form.[2] CKD is characterized by the gradual, irreversible loss of kidney function, leading to the accumulation of waste and fluids in the body. This condition arises from factors such as diabetes, hypertension, infections, autoimmune diseases, and genetic disorders, with diabetes and hypertension being the most common causes.[3]

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In addition to systemic effects such as appetite and weight loss, fatigue, headache, hematuria, edema due to fluid retention, and electrolyte imbalances, CKD can present with a range of dermatological changes, often due to fluid and electrolyte imbalance, impaired hormone production, and the accumulation of waste products in the blood.[4] These changes include leukonychia, melanonychia, half-nail signs, xerosis, hyperpigmentation, pallor, pruritus, infectious diseases, skin thinning, and ecchymosis.[5]

Xerosis and pruritus are common dermatological symptoms in CKD patients, and while the exact mechanisms are not fully understood, several factors contribute to their development. Imbalances in electrolytes, especially calcium and phosphate, lead to the accumulation of these substances in the skin and blood vessels. Additionally, impaired kidney hormone production can affect skin glands, leading to dryness and increased infection risk.[5] Although previous theories pointed to histamine release as the cause of pruritus in CKD, current views suggest a non-histaminergic pathway as the underlying mechanism.[6,7]

Chronic pruritus is an unpleasant sensation associated with wanting to scratch, lasts more than 6 weeks, and is a common and potentially debilitating symptom in CKD patients.[7] It is often associated with anxiety, depression, and sleep disturbances, and severe pruritus has been identified as an independent risk factor for increased mortality and poor prognosis.[8] The pattern of pruritus in CKD tends to be widespread, intermittent, and symmetric, often affecting the legs, back, and scalp, with a tendency to worsen at night. Unlike other causes, CKD-related pruritus has no primary skin lesion but may lead to secondary excoriations due to chronic scratching.[7]

Inflammatory markers are known to correlate with CKD, and their presence contributes to kidney damage and the development of associated symptoms. Elevated inflammatory markers in CKD are also linked to fatigue, reduced appetite, and increased risks of both mental and physical dysfunction. Given the significant relationship between CKD and inflammation, it is crucial to explore how inflammatory markers might impact dermatological changes in CKD patients.[9]

This study aims to evaluate the impact of inflammation on xerosis and pruritus in CKD patients and investigate the connection between these markers and dermatological findings. The results may help develop new approaches to optimizing renal and dermatological management strategies in CKD patients.

Materials and Methods

This cross-sectional and observational study received approval from the Non-Interventional Clinical Research Ethics Committee of Uşak University Faculty of Medicine (approval number: 386-386-08, date: 06.06.2024).

Patients aged 18 years or older with a confirmed diagnosis of CKD, and giving informed consent to participate, were included in the study. CKD diagnosis is based on the "2024 Kidney Disease: Improving Global Outcomes" guidelines.[10] Patients with other inflammatory dermatological conditions causing xerosis and pruritus, active infections, inflammatory diseases, or those using medications or having conditions likely to elevate inflammatory markers were excluded from the study.

Age, sex, dialysis status, and physical examination findings such as xerosis and pruritus of the patients were demographic and clinical variables that were analyzed. The severity of xerosis was assessed using a clinical grading scale proposed by Weber et al.[11] This scale evaluates two main parameters: visible dryness and tactile roughness, each scored from 0 (absent) to 4 (extreme). A higher score indicates greater severity of xerosis, integrating visual and tactile clinical observations.

- **Score 0 (absent):** No visible dryness; skin is perfectly smooth and pliable.
- **Score 1 (slight):** Slight scaling and dull appearance with slightly irregular and rough tactile evaluation.
- **Score 2 (moderate):** Presence of minor scales, whitish appearance, and definite roughness; tactile evaluation shows irregularity and slight stiffness.
- **Score 3 (severe):** Uniformly distributed small and larger scales, redness, and some superficial cracks; advanced irregularity and rough feeling with associated stiffness.
- **Score 4 (extreme):** Dominated by large scales, redness, cracks, and eczematous changes; gross irregularity and severe disturbance of skin markings with definite stiffening.

Pruritus severity was evaluated with a 10-point Visual Analog Scale (VAS), where 0 represents no pruritus, and 10 indicates the worst imaginable pruritus.

Blood samples were analyzed for C-reactive protein (CRP) and complete blood count with differentials. Systemic inflammatory indices were calculated:

- **Systemic Inflammation Index (SII):** Neutrophil × Platelet/Lymphocyte.
- **Systemic inflammatory response index (SIRI):** Neutrophil × Monocyte/Lymphocyte.
- **Aggregate index of systemic inflammation (AISI):** Neutrophil × Platelet × Monocyte/Lymphocyte.
- **Neutrophil-to-lymphocyte (NLR) ratio:** Neutrophil/Lymphocyte.

- **Derived neutrophil-to-lymphocyte (dNLR) ratio:** Neutrophil/(WBC - neutrophil).
- **Platelet-to-lymphocyte (PLR) ratio:** Platelet/Lymphocyte.
- **Monocyte-to-lymphocyte (MLR) ratio:** Monocyte/Lymphocyte.
- **Platelet-to-monocyte (PMR) ratio:** Platelet/Monocyte.

The data of included participants were anonymized and recorded in Microsoft Excel for further analysis. The data were analyzed using IBM SPSS v23.0 (Armonk, NY: IBM Corp.).

The chi-square test was used for categorical variables, including the association between xerosis and pruritus or dialysis status. The correlation between xerosis and pruritus severity was evaluated using Spearman's rank correlation coefficient (Rho). Comparisons of inflammatory markers between groups (pruritus vs. no pruritus, dialysis vs. non-dialysis) were conducted using appropriate statistical tests, including independent samples t-test for normally distributed data and Mann-Whitney U test for non-normal distributions. It was determined that at least 28 participants were required to obtain a moderate effect size (d = 0.5) with 95% power and 5% type I error, applying the finite-population correction. A *p*-value < 0.05 was considered statistically significant.

Results

The study included 92 adult patients diagnosed with CKD, of whom 47 (51.1%) had xerosis and/or pruritus. The demographics and clinical characteristics of patients are shown in Table 1. All patients but one with pruritus had both xerosis and pruritus (n = 34, 97.1%). Thirteen patients with xerosis (28%) did not experience pruritus. Xerosis and pruritus were significantly associated ($P < 0.001$, chi-square statistic X = 47.953). The severity of xerosis and the severity of pruritus were significantly and positively correlated (Rho = 0.454, $P < 0.001$).

The Effect of Dialysis on Xerosis and Pruritus

Dialysis was administered to 44 patients, accounting for 47.8% of the total cohort. Xerosis was present in 47 (51.1%) patients, while 35 (38%) patients had pruritus. The proportion of dialyzed patients with xerosis was higher than that of non-dialyzed patients (59.6% vs. 39.6%, $P = 0.021$). Xerosis severity was not associated with dialysis ($P = 0.121$). Pruritus was similar in dialyzed and non-dialyzed patients (38.6% vs. 37.5%, $P = 0.911$), and pruritus severity was not associated with dialysis ($P = 0.227$).

Table 1. The demographics and clinical characteristics of patients

Characteristics	Total (n = 92)
Age, mean (SD)	69.1 (12.8)
Sex, n (%) Female	 46 (50%)
Dialysis, n (%) Yes	 44 (47.8%)
Xerosis, n (%) Yes	 47 (51.1%)
Xerosis severity, n (%) 0 (no xerosis) 1 (mild) 2 (moderate) 3 (severe) 4 (very severe)	 45 (48.9%) 26 (28.3%) 15 (16.3%) 4 (4.3%) 2 (2.2%)
Pruritus, n (%) Yes	 35 (38%)
Pruritus VAS score, median (IQR)	8 (4)
Pruritus severity (VAS), n (%) No pruritus Mild (< 4) Moderate (4 ≤ -< 7) Severe (7 ≤ -< 9) Very severe (≥ 9)	 57 (62%) 7 (7.6%) 4 (4.4%) 13 (14.1%) 11 (11.9%)

SD: standard deviation, VAS: Visual analog scale, IQR: Interquartile range

The Association Between Inflammatory Markers with Pruritus and with Xerosis

White blood cells, neutrophils, lymphocytes, platelets, and monocytes counts were not different between patients with and without xerosis, and there was no significant association between inflammatory markers and xerosis.

White blood cell, neutrophils, lymphocytes, platelets, and monocytes counts were not different between patients with and without pruritus. The median monocyte-to-lymphocyte (MLR) of patients with pruritus was significantly higher than that of those without ($P = 0.037$) (Figure 1). No other significant association regarding inflammatory markers was observed between the patients with and without pruritus. Pruritus VAS score was significantly correlated with MLR (Rho = 0.206, $P = 0.049$). The comparison of CRP and inflammatory indices between the patients with and without pruritus is shown in Table 2.

The Association Between Inflammatory Markers with Dialysis Status

White blood cells, neutrophils, lymphocytes, platelets, and monocytes counts showed no significant differences between patients undergoing dialysis and those not receiving dialysis. The median CRP of the patients on dialysis was significantly higher than that of those not on dialysis (P = 0.046).

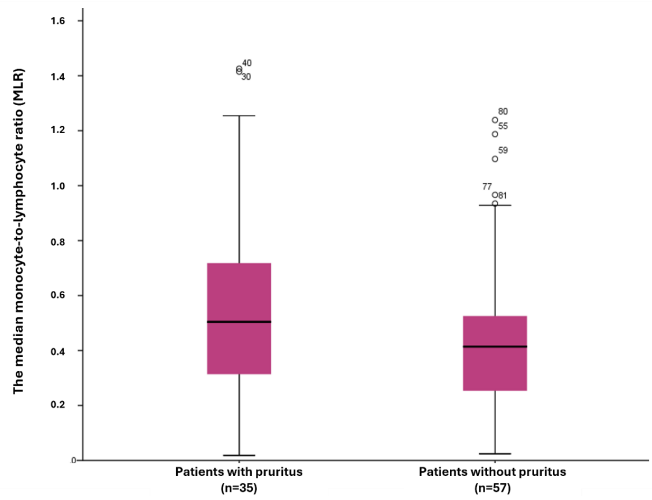

Figure 1. The median monocyte-to-lymphocyte ratio (MLR) was significantly higher in patients with chronic kidney disease-associated pruritus than those without (P = 0.037)

No other significant association with inflammatory markers was observed regarding the dialysis status of the patients (Table 4). The mean MLR levels of patients with pruritus (0.7±0.3) were significantly higher than the mean MLR levels of patients without pruritus (0.4±0.2) among dialyzed patients (P = 0.007).

Discussion

Pruritus and xerosis are the two most common cutaneous manifestations affecting approximately 70% of patients with CKD.[8] The mechanism underlying CKD-associated pruritus remains to be understood. The accumulation of uremic toxins, the release of histamine from mast cells, the imbalance of opioids, the disruption of the epidermal barrier, and the release of inflammatory factors are thought to be primary causes of CKD-associated pruritus.[12] However, it has been recently shown that hyperparathyroidism, hyperphosphatemia, hypercalcemia, and clearance of uremic toxins through adequate dialysis do not correlate with pruritus in CKD. [13] Besides, antihistamines have minimal therapeutic efficacy on pruritus in patients with CKD.[12] Therefore, we investigated the effects of inflammation on CKD-associated cutaneous manifestations, especially on pruritus. We found that pruritus with or without xerosis in patients with CKD was associated with increased MLR levels.

Table 2. Inflammatory markers regarding xerosis and pruritus status

	All (n = 92)	Xerosis (n = 47)	No xerosis (n = 45)	*P* value	Pruritus (n = 35)	No pruritus (n = 57)	*P* value
CRP, median (IQR)	39.6 (90.1)	35.2 (79.1)	48.7 (107.15)	0.303	26.8 (79.1)	56.9 (92.6)	0.335
NLR, median (IQR)	6.3 (5.3)	5.8 (5.7)	3.9 (4.05)	0.082	6.1 (7.1)	4.5 (4.3)	0.064
dNLR, median (IQR)	3.0 (2.4)	3.3 (2.4)	2.4 (2.3)	0.175	3.4 (2.5)	2.8 (2.1)	0.140
PLR, median (IQR)	178.1 (154.5)	188.7 (158.0)	159.5 (148.8)	0.794	188.7 (165.1)	174.8 (143.2)	0.544
MLR, median (IQR)	0.5 (0.4)	0.5 (0.4)	0.4 (0.3)	0.301	**0.5 (0.4)**	**0.4 (0.3)**	**0.037**
PMR, median (IQR)	419.5 (280.8)	397.0 (272.2)	438.6 (255.9)	0.458	377.3 (259)	454.3 (370.7)	0.167
SII, median (IQR)	1121.5 (1517.4)	1398.8 (1828.6)	1080.1 (1260.2)	0.451	1398.8 (2058.1)	1080.1 (1195.8)	0.301
SIRI, median (IQR)	3.1 (3.3)	3.2 (3.9)	2.5 (2.8)	0.371	3.6 (4.9)	2.4 (2.8)	0.079
AISI, median (IQR)	695.2 (1049.8)	676.5 (1142.7)	713.9 (873.1)	0.922	856.3 (1118.3)	527.4 (883.3)	0.325

The significant associations were marked in bold
CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, dNLR: Derived neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, PMR: Platelet-to-monocyte ratio, SII: Systemic immune inflammation response index, SIRI: Systemic inflammatory response index, AISI: Aggregate index of systemic inflammation, IQR: Interquartile range

Table 3. Inflammatory markers regarding pruritus status in patients with xerosis

	All (n = 47)	Pruritus (n = 34)	No pruritus (n = 13)	*P* value
CRP, median (IQR)	35.2 (79.1)	30.6 (86.6)	64.7 (72.7)	0.905[a]
NLR, mean (SD)	6.7 (4.4)	7.2 (4.6)	5.4 (3.7)	0.219[b]
dNLR, median (IQR)	3.3 (2.4)	3.5 (2.4)	3.1 (2.0)	0.341[a]
PLR, median (IQR)	188.7 (158.0)	193.8 (169.2)	181.0 (163.0)	0.405[a]
MLR, mean (SD)	0.5 (0.4)	**0.6 (0.4)**	**0.4 (0.2)**	**0.046[b]**
PMR, median (IQR)	397.0 (272.2)	356.2 (263.8)	468.3 (379.1)	0.244[a]
SII, mean (SD)	1575.4 (1301.4)	1740.3 (1433.8)	1143.9 (749.0)	0.162[b]
SIRI, mean (SD)	3.9 (3.2)	4.5 (3.4)	2.5 (1.9)	0.051[b]
AISI, median (IQR)	676.5 (1142.7)	896.5 (1129.1)	414.2 (661.5)	0.101[a]

The significant associations were marked in bold
[a]Independent samples Mann-Whitney U test
[b]Independent samples T-test
CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, dNLR: Derived neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, PMR: Platelet-to-monocyte ratio, SII: Systemic immune inflammation response index, SIRI: Systemic inflammatory response index, AISI: Aggregate index of systemic inflammation, IQR: Interquartile range

Table 4. Inflammatory markers regarding dialysis status

	All (n = 92)	Dialysis (n = 44)	No dialysis (n = 48)	*P* value
CRP, median (IQR)	39.6 (90.1)	**66.4 (104.8)**	**26.3 (71.3)**	**0.046[a]**
NLR, median (SIQR)	6.3 (5.3)	5.9 (5.3)	4.4 (4.4)	0.332[a]
dNLR, median (IQR)	3.0 (2.4)	3.4 (2.8)	2.7 (1.9)	0.220[a]
PLR, median (IQR)	178.1 (154.5)	159.1 (139.9)	202.1 (180.3)	0.270[a]
MLR, median (IQR)	0.5 (0.4)	0.5 (0.4)	0.5 (0.3)	0.725[a]
PMR, median (IQR)	419.5 (280.8)	337.5 (302.2)	438.7 (232.7)	0.088[a]
SII, median (IQR)	1121.5 (1517.4)	1016.2 (1193.9)	1329.5 (1647.5)	0.511[a]
SIRI, median (IQR)	3.1 (3.3)	3.1 (3.0)	3.0 (3.6)	0.737[a]
AISI, median (IQR)	695.2 (1049.8)	520.1 (809.2)	830.2 (1154.6)	0.220[a]

The significant associations were marked in bold
[a]Independent samples Mann-Whitney U test
[b]Independent samples T-test
CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, dNLR: Derived neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, PMR: Platelet-to-monocyte ratio, SII: Systemic immune inflammation response index, SIRI: Systemic inflammatory response index, AISI: Aggregate index of systemic inflammation, IQR: Interquartile range

Xerosis, affecting nearly 85% of individuals with CKD, stands as one of the most common dermatological manifestations associated with pruritus.[14] The present study found that pruritus and xerosis were strongly associated and positively correlated, but 28% of patients with xerosis did not have pruritus. Patients with xerosis relieved of pruritus by moisturizers, but some patients with marked xerosis not accompanied by pruritus, suggests that dry skin is probably not an etiologic factor per se, but rather a factor that increases the sensation of pruritus in patients with CKD.

Our study showed no significant association between hemodialysis and pruritus or pruritus severity. Xerosis was more common in patients on dialysis but was not related to the severity of the condition. Numerous studies have evaluated the effect of dialysis on pruritus in CKD patients. According to earlier findings in real-world observational research from The Dialysis Outcomes and Practice Patterns Study (DOPPS), pruritus in patients with CKD occurs in up to 80% of hemodialyzed participants, with approximately 40% of them experiencing moderate to severe itching.[16] A recent large-scale study from DOPPS, including 6256 hemodialysis patients, has shown that optimal dialysis has only slightly reduced the high prevalence of pruritus among dialysis patients.[13] Based on these findings, we conclude that uremic toxins, such as creatinine, urea, nitrogen, and others, are not the only cause of pruritus. However, they may contribute to it in those with CKD.

Inflammatory markers such as o neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte ratio (PLR) MLR reflect a low-grade inflammatory state in the body and have been commonly evaluated as biomarkers of cardiovascular diseases and malignant conditions.[17] In our study, CKD patients with pruritus had higher MLR values than those without pruritus. However, we did not observe a significant difference in inflammatory markers between patients with and without xerosis among CKD patients. When we evaluated the relationship between pruritus and MLR in patients with xerosis only, we found that the MLR of pruritic patients was higher than that of non-pruritic patients. A previous study from Türkiye reported that PLR values were significantly lower in dialysis patients with pruritus compared to those without pruritus. MLR was not evaluated in this study.[18] We found no other study evaluating pruritus and inflammatory markers in CKD patients. A study evaluating pruritus in mycosis fungoides patients showed no relationship between pruritus and MLR.[19]

In a population-based study comparing 3,015 CKD patients with 8,247 non-CKD individuals, MLR was higher in CKD patients. This study also showed that MLR was associated with cardiovascular and all-cause mortality in CKD patients and had the highest predictive value compared to other factors.[20] Patients with moderate to extreme pruritus have also been shown to be at higher risk for death or transfer to hemodialysis.[21] Another large-scale study reported that MLR is a marker that can strongly predict the risk of new-onset CKD.[22] Moreover, MLR was significantly and independently associated with inflammation and disease severity in individuals with CKD.[23] Considering the higher MLR levels in pruritic patients observed in our study, it can be inferred that inflammation plays a significant role in the pathogenesis of pruritus in CKD patients. In order to prevent poor health outcomes and mortality, patients with pruritus and elevated MLR levels should be monitored more closely.

If inflammation is associated with pruritus in CKD patients, why is it only MLR associated with pruritus and not NLR, PLR, or CRP? The elevated levels of MLR in pruritic CKD patients suggest that monocytes may be involved in the mechanism of uremic pruritus. In CKD, monocytes play a significant role in low-grade chronic inflammation. Proinflammatory cytokines like interleukin-1β (IL-1β), tumor necrosis factor-alpha, and IL-6 are secreted by these cells.[24] Upon examining the relationship between dialysis and inflammatory markers, CRP levels were found to be elevated in dialysis patients, but MLR levels were similar between non-dialyzed and dialyzed patients. MLR levels were higher again in dialysis patients with pruritus compared to those without it. In a previous study, a larger proportion of intermediate monocytes (CD14++, CD16+) independently predicted pruritus intensity in patients receiving hemodialysis. The findings imply that uremic pruritus may be related to altered monocytic phenotypes.[25]

Study Limitations

The study had limitations. Since it is cross-sectional and observational, causality cannot be established. The results may not be generalizable due to the small sample size and the study being conducted in a single center. The severity of CKD, comorbidities, and complications such as cholestasis, diabetes, anemia, as well as medications that may cause pruritus other than due to xerosis, may be confounding factors and are not evaluated in this study.

Conclusion

In conclusion, we reported a strong association of pruritus with elevated MLR levels in CKD patients. More structured studies investigating the role of monocytes in CKD-related pruritus are warranted. Monocytes appear to be central players in inflammation, pruritus, and mortality in CKD. Therefore, therapeutic approaches to reduce monocyte activity may be used in the management of CKD-associated pruritus and CKD in general.

Ethics

Ethics Committee Approval: The study received approval from the Non-Interventional Clinical Research Ethics Committee of Uşak University Faculty of Medicine (approval number: 386-386-08, date: 06.06.2024).

Informed Consent: Patients aged 18 years or older with a confirmed diagnosis of CKD, and giving informed consent to participate, were included in the study

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.D.Ö, O.V.Ç, N.İ, Z.A, E.H, Concept: N.D.Ö, O.V.Ç, N.İ, Z.A, E.H, Design: N.D.Ö, O.V.Ç, Data Collection or Processing: N.D.Ö, O.V.Ç, N.İ, Z.A, E.H, Analysis or Interpretation: N.D.Ö, O.V.Ç, N.İ, Literature Search: N.D.Ö, O.V.Ç, N.İ, Writing: N.D.Ö, O.V.Ç.

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