Research Article (Araştırma Makalesi)

Evaluation of Hematological Indices in Acromegalic Patients

Akromegali Hastalarında Hematolojik İndekslerin Değerlendirilmesi

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Özet

Amaç: Akromegali, genellikle hipofiz adenomu tarafından salgılanan otonom büyüme hormonu (BH) fazlalığı ile giden bir hastalıktır. Akromegalide mortalitenin ana nedeni serebrovasküler, kardiyovasküler, solunum olayları ve malignitelerdir. Nötrofil/lenfosit oranı (NLR), monosit/lenfosit oranı (MLR), eritrosit dağılım genişliği (RDW) ve trombosit dağılım genişliği (PDW), Delta nötrofil indeks (DNİ) popüler inflamasyon markerlarıdır. Bu çalışmada akromegali hastalarında tedavi öncesi ve sonrasında IGF-1, BH, DNİ, NLR, MLR, RDW ve PDW parametrelerini inceleyerek değerlendirmeyi ve akromegali tedavisinin bu parametreler üzerindeki etkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Hastanemiz Endokrinoloji polikliniğinde Nisan 2014 -Şubat 2022 yıllarında takip ve tedavi edilen akromegali hastalarının dosyalarından ve hastane kayıtlarından yaş, cinsiyet, ek hastalıkları, kullandığı ilaçlar, tam kan sayımı, böbrek fonksiyon testleri, karaciğer fonksiyon testleri, patoloji sonuçları, tümör boyutları, ek komorbiditelerini kaydederek sonuçlarını değerlendirdik. Tedavi öncesi ve sonrasında rutin olarak elde edilmiş olan IGF-1, BH, DNİ, NLR, MLR, RDW ve PDW düzeylerini inceleyerek karşılaştırdık.

Bulgular: Çalışmaya alınan toplam 26 hastanın, 12 si kadın (%46), 14 ü erkek (%53) idi. Hastaların yaşları 25 ile 79 (ortalama: 53.73±16.21) arasındaydı. Hastaların 11 tanesinin (%42) tip 2 diyabetes mellitus, 9 tanesinin (%34) hipertansiyon tanısı mevcuttu. Hastaların cerrahi öncesi aktif hastalık döneminde ve cerrahi sonrası kür olan hastaların 6. aydaki değerleri ile cerrahi sonrası remisyona girmeyen medikal tedavi alan hastaların, tedavi sonrası BH, IGF-1, NLR, DNI, PDW, RDW değerlerinde tedavi öncesi değerlere göre istatistiksel olarak anlamlı düşüş izlendi. M/L oranında da tedavi sonrası değerler tedavi öncesi değerlere göre düşmüştü fakat istatiksel olarak anlamlı değildi. Akromegali hastalarında tanı anındaki IGF-1 düzeyi ile NLR, RDW, PDW arasında istatiksel olarak anlamlı bir ilişki saptanmadı.

Sonuç: Akromegalide kardiyovasküler hastalık sıklığı ve kardiyovasküler risk faktörleri artmıştır. Akromegali hastalarında dolaşımdaki inflamatuar belirteçlerin düzeyleri ve bunların tedaviyle ilişkisi üzerine yapılan çalışmalar çelişkilidir. Bizim çalışmamızda GH, IGF-1, NLR, DNI, PDW, RDW değerlerinde tedavi öncesinde tedavi sonrasına göre yüksek değer saptanmıştır. Yüksek seviyelerde IGF-1'e uzun süreli maruz kalmanın, NLR gibi inflamutuar belirteçlerde artış ve aterosklerotik riskte artma ve buna bağlı olarak artmış kardiyovasküler riske de yol açabileceğini düşündürmektedir. Kontrolsüz hastalığa bağlı subklinik inflamasyondaki artışlar, akromegali hastalarında artan morbidite ve mortaliteye katkıda bulunabilir. Bu nedenle akromegalide erken tanı ve tedavi çok önemlidir.

Anahtar kelimeler: Akromegali, Delta nötrofil indeks, Monosit/lenfosit oranı, Nötrofil/lenfosit oranı

Abstract

Objective: Acromegaly is a chronic systemic disease characterized by autonomous and excessive secretion of growth hormone (GH). Acromegaly is most commonly caused by ais a somatotroph adenoma of the anterior pituitary. In acromegaly, mortality primarily results from are cerebrovascular, cardiovascular, respiratory diseases and malignancies. Monocyte/lymphocyte ratio (MLR), neutrophil/lymphocyte ratio (NLR), red cell distribution width (RDW), platelet distribution width (PDW) and delta neutrophil index (DNI) are popular inflammatory markers. This study's purpose was to assess pre/post-treatment levels of NLR, GH, RDW, MLR, PDW and DNI in acromegalic patients and to investigate the impact of acromegaly treatment on these markers.

Materials and Methods: Twenty-six patients with acromegaly, treated and followed at our endocrinology outpatient clinic between April 2014 and February 2022 were included in the study. Age, sex, comorbidities, medications, complete blood count, kidney and liver function tests, pathology reports, tumor size, pre/post-treatment levels of IGF-1, GH, DNI, NLR, MLR, RDW and PDW were retrieved from patients' files and outcomes were evaluated.

Results: Among 26 patients included in the study, 12 (46%) were female and 14 (53%) were male. The average age of the patients was 53.73±16.21 years (range, 25-79). There were 11 (42%) patients with type 2 diabetes mellitus and 9 (34%) patients with hypertension. A statistically significant reduction was observed in post-operative GH, IGF-1, NLR, DNI, PDW and RDW values compared to preoperative values (during active disease phase) and at 6 months in patients with postoperative cure, and compared to pretreatment values in patients without postoperative remission who received medical treatment. A reduction was also observed in post-treatment MLR compared to pretreatment ratio but the difference was non-significant. There was no statistically significant correlation between the IGF-1 levels at the time of diagnosis and NLR, RDW, PDW in patients with acromegaly.

Conclusion: Studies on the values of circulating inflammatory biomarkers in patients with acromegaly and their relationship to treatment remain unclear. In our study, higher pre-treatment GH, IGF-1, NLR, DNI, PDW, RDW values were found compared to post- treatment. This suggests that having chronically higher than normal values of IGF-1 may also lead to increased inflammatory markers such as NLR and increased atherosclerotic risk. Chronic subclinical inflammation caused by uncontrolled disease might lead to an increase in mortality and morbidity in acromegalic patients. Therefore, early diagnosis and treatment of acromegaly are crucial.

Keywords: Acromegaly, neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio, delta neutrophil index.

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INTRODUCTION

Acromegaly is caused by unrestrained secretion of growth hormone (GH) and insulin-like growth factor (IGF)-1. The prevalence and incidence of acromegaly are not clearly known (1). In an epidemiological study, prevalence estimates ranging from 2.8 to 13.7 cases/100.000 people and an annual incidence of 0.2-1.1 cases/100.000 people have been reported (2). Insulin-like growth factor-1 (IGF-1) and GH promote cell growth through several biochemical pathways, resulting in mortality and severe morbidity. In acromegaly, mortality primarily results from cardiovascular, cerebrovascular, respiratory diseases and malignancies (3).

Delta neutrophil index (DNI) represents the number of immature granulocytes which are not normally present in peripheral blood. DNI is a common term that refers to granulocyte precursors including myelocytes, promyelocytes and metamyelocytes found in bone marrow. DNI and elevated immature granulocyte (IG) count indicate activation of bone marrow. Delta neutrophil index which reflects an increase in immature granulocytes in infectious and inflammatory events also contributes to changes in WBC (white blood cell) count (4). DNI has been used in patient populations with conditions predominantly associated with inflammatory process such as sepsis, acute appendicitis, meningitis, decompensated heart failure, acute gout attack and acute pancreatitis in a number of studies, which suggested that it can provide guidance to clinicians about disease severity (5). PDW, RDW, NLR and MLR are inflammatory biomarkers obtained from a routine complete blood cell count (CBC). There is a growing interest in these markers. Several studies have demonstrated that these subclinical inflammatory markers are correlated with complications of many other diseases including diabetes mellitus (6,7), ischemic heart disease (8,9) and malignancies (10,11).

As far as we know, the correlation of DNI with treatment has not been studied in acromegalic patients. Thus, in this study, we aimed to analyze DNI, NLR, MLR, RDW and PDW before and after treatment in acromegalic patients and to investigate the impact of acromegaly treatment on these parameters.

MATERIALS AND METHODS

Ethics committee approval was obtained from Ethics Committee of the Healthcare Application and Research Hospital of Kahramanmaras Sutcu Imam University (date: 23.02.2022; session no: 2022/04; decision no: 06) prior to initiation of the study. The institutional review board approved this retrospective study and waived the informed consent requirement. This study was conducted in accordance with the Principles of the Declaration of Helsinki.

Medical charts and hospital records of acromegalic patients treated and followed at the Endocrinology outpatient clinic of our hospital between April 2014 and February 2022 were reviewed retrospectively. Age, sex, comorbidities, medications, Complete Blood Count (CBC), kidney function tests, liver function tests, pathology reports, tumor dimensions and comorbidities of the patients were retrieved and outcomes evaluated. Pre/post-treatment levels of IGF-1, BH, DNI, NLR, MLR, RDW and PDW were compared.

The diagnosis of acromegaly was made based on typical clinical characteristics and confirmed by measuring high GH levels after oral glucose loading and increased IGF-1 levels for sex and age.

Among 26 acromegalic patients included in the study, none had comorbid conditions that could adversely affect the course and results of the study, including an active infection, chronic infection, rheumatic diseases, chronic kidney failure, malignancy and chronic obstructive pulmonary disease.

IGF-1, GH, DNI, monocyte, neutrophil, RDW and PDW values of acromegalic patients were recorded during the active disease phase preoperatively and at 6 months postoperatively, and after medical therapy in patients without surgical cure. Postoperative cure was defined as an IGF-1 within normal range for sex and age and a GH level of <1 ng/ml on post-operative Oral Glucose Tolerance Test (OGTT). Disease in remission was defined as an IGF-1 value within normal range for sex and age following pharmacological treatment.

Laboratory Workup

Serum growth hormone concentrations was measured in blood samples obtained at 8 am after overnight fasting using electrochemiluminescence immunoassay (ECLIA) (human GH kit, Architect c8000 Chemistry Analyzer, Abbott Diagnostics). The diagnosis of acromegaly was confirmed by measuring growth hormone levels at every 30 minutes over a total duration of 120 minutes following glucose administration (75 grams) after overnight fasting.

Serum total Insulin-like growth factor 1 was obtained using immunometric chemiluminescence assay (IMMULITE 2000, Siemens, Washington, D.C., USA).

Neutrophil (3.39-8.86 x 103µl), lymphocyte (1.05-3.17 x 103 µl) and monocyte (0.22-0.68 x 103 µl) counts, and RDW (11.2-14%) and PDW (9.5-15), DNI (0.01-0.04) were obtained using an automated hematological analyzer (XN3000; Sysmex Corp., Kobe, Japan). Neutrophil/lymphocyte ratio (NLR) and monocyte/

lymphocyte ratio (MLR) were calculated manually. The immature granulocyte fraction includes myelocytes, metamyelocytes and promyelocytes but not myeloblasts or band neutrophils.

NLR, MLR, PDW, RDW and DNI values of acromegalic patients obtained during the preoperative active disease phase and preoperatively and at 6 months postoperatively for patients achieving postoperative cure, and preoperatively and after completion of medical treatment for patients without postoperative cure were compared. The aforementioned parameters were compared before and after medical treatment for three patients who did not undergo surgery.

Statistical Analysis

SPSS, version 19 software (IBM Corp., Armonk, NY) was used for statistical analyses. The Kolmogorov–Smirnov test was used to check the normality of data. Non-parametric tests were used since the data were non-normally distributed. The variables were also analyzed using Pearson and exact chi-square tests. Spearman's correlation test was used to examine the correlation between variables. If p value was <0.05, it was considered statistically significant.

RESULTS

We presented 26 acromegaly patients. The mean age of the patients was 53.73±16.21 years (range, 25-79), 53% (n=14) were male and 47% (n=12) were female. There were 11 (42%) patients with type 2 diabetes mellitus (DM) and 9 (34%) patients with hypertension.

Except for 3 patients who were medically treated because of advanced age and refusal of surgery, all other patients (n=23) underwent transsphenoidal pituitary surgery. Postoperative cure was achieved in 6 (23%) patients. 12 patients were treated with SSAs (somatostatin analogues) alone and 6 patients received SSA treatment in combination with dopamine agonist cabergoline. Disease control was achieved after surgery in 14 patients. Remission was achieved with medical treatment (SSA and cabergoline) in 3 patients who did not undergo surgery. Remission was achieved in a total of 17 (65%) patients. Despite surgery and maximum medical treatment, disease control couldn't be achieved in 3 (11%) patients.

A statistically significant reduction was observed in post-operative GH, IGF-1, NLR, DNI, PDW and RDW values compared to preoperative values (during active disease phase) and at 6 months in patients with postoperative cure, and compared to pretreatment values in patients without postoperative remission who received medical treatment (**Table 1**).

For MLR, post-treatment values also showed a reduction versus pre-treatment values, although the difference was not statistically significant. At the time of diagnosis, IGF-1 level was not significantly associated with NLR, RDW and PDW in acromegalic patients (**Table 2**).

DISCUSSION

Studies in acromegalic patients have reported conflicting findings on the inflammatory biomarkers in serum and their correlation with treatment (12,13). White blood cell (WBC), lymphocyte, monocyte, neutrophil, immature granulocyte and platelet counts are established indicators of inflammation (14). In addition to WBC count, MLR and NLR are potential markers that indicate immune response and inflammation. MLR and NLR, novel markers, proved superior to neutrophil, monocyte, lymphocyte, leukocyte and platelet counts in the assessment of inflammation. A number of studies have reported that NLR and MLR are positively correlated with traditional markers of inflammation.

Table 1. Pre-treatment vs post-treatment comparison of hematological and biochemical parameters

	n	Pre-treatment (mean±SD)	Post-treatment (mean±SD)	p
IGF-1	26	640.19±280.83	212.46±128.19	0.0001*
GH	26	9.64±7.69	1.63±3.05	0.0001*
NLR	26	2.36 ±0.92	1.93±0.59	0.011*
MLR	26	0.24±0.09	0.23±0.09	0.492
DNI	26	0.04±0.02	0.028±0.02	0.001*
RDW	26	14.22±1.19	13.17±0.77	0.0001*
PDW	26	20.17±12.51	11.74±1.62	0.0001*

*Statistically significant. GH, growth hormone; IGF-1, Insulin-like Growth Factor-1; NLR, Neutrophil-to-lymphocyte ratio; MLR, monocyte-to- lymphocyte ratio; DNI, delta neutrophil index; RDW, red cell distribution width; PDW, platelet distribution width; SD, standard deviation.

Table 2. Relationship of IGF-1 level with GH, RDW, PDW, NLR, DNI and MLR

Variables		IGF-1	GH	RDW	PDW	NLR	DNI	MLR
IGF-1	**r**	1	0,109	0,109	0,086	-0,58	-0,105	-0,157
	p		0,349	0,597	0,675	0,778	0,609	0,443
GH	**r**	0,109	1	-0,264	0,350	-0,12	-0,308	-0,117
	p	0,349		0,193	0,080	0,954	0,421	0,569
RDW	**r**	0,109	0,109	1	-0,128	0,328	0,166	0,146
	p	0,597	0,193		0,532	0,102	0,670	0,477
PDW	**r**	0,086	0,350	-0,128	1	-0,252	-0,614	-0,278
	p	0,675	0,080	0,532		0,214	0,079	0,169
NLR	**r**	-0,58	-0,12	0,328	-0,252	1	0,223	0,574
	p	0,778	0,954	0,102	0,214		0,565	0,020
DNI	**r**	-0,105	-0,308	0,166	-0,614	0,223	1	0,058
	p	0,609	0,451	0,670	0,079	0,565		0,083
MLR	**r**	-0,157	-0,117	0,146	-0,278	0,574	0,058	1
	p	0,043	0,569	0,477	0,169	0,020	0,083	

IGF-1, Insulin-like Growth Factor-1; GH, growth hormone; NLR, Neutrophil/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; DNI, delta neutrophil index; RDW, red cell distribution width; PDW, platelet distribution width

Moreover, large studies have reported the predictive power of MLR and NLR in some diseases such as DM, acute coronary syndrome and a multitude of cancers (15,16). PDW and RDW represent diameter differences in platelets and erythrocytes, respectively, and have been identified as inflammatory markers in several studies (17,18).

Immature granulocytes indicate increased production of myeloid cells. An increase in the amount of granulocytes occurs in the presence of infectious and inflammatory conditions. DNI is a novel inflammatory biomarker that reflects circulating IG fractions (4). In previous studies, DNI has been used utilized for the assessment of many infectious diseases (e.g., sepsis, pneumonia) and non-infectious inflammatory responses (the risk of cardiac mortality after acute myocardial infarction) (19–21).

Boero et al. investigated inflammatory biomarkers in patients with active acromegaly and healthy subjects. They reported higher concentrations of ceruloplasmin, endothelin, OxLDL and thiobarbituric acid reactive substance (TBARS) but comparable levels of myeloperoxidase, paraoxonase-1, superoxide dismutase and platelet-activating factor acetylhydrolase (PAF-AH) in acromegalic patients versus control group (22).

In a separate study, Arikan et al. looked at the effect of persistent elevation of IGF-1 and GH levels on inflammatory markers and reported higher values of tumor necrosis factor (TNF)-alpha and interleukin (IL)-8, IL-1, IL-2, IL-6, IL-10, hsCRP and homocysteine in acromegalic patients compared to control group (23).

Limited literature data are available on the relationship between chronic inflammation and acromegaly. Ünübol et al. reported a significantly higher MPV in patients with acromegaly versus controls and found a positive correlation between MPV and IGF-1 values (24).

In a study by Üçler et al., IGF-1 levels were positively correlated with NLR. The authors suggested that chronic high IGF-1 levels may result in increased risk of atherosclerosis and hence, increased cardiovascular risk, caused by high inflammatory biomarkers such as NLR (25). Chronic subclinical inflammation caused by uncontrolled disease may be associated with high rates of morbidity and mortality. In the current study, IGF-1 at the time of diagnosis was not significantly associated with NLR, DNI, RDW and PDW.

In another study, NLR was observed to be lower than preoperative levels in patients with acromegaly who had healed after operation. MLR also decreased postoperatively but the difference was non- significant. In patients with remission after medical treatment, preoperative and post-treatment PDW, RDW, NLR and MLR values were comparable (26).In contrast, in our study, a significant decrease was found in GH, IGF-1, NLR, DNI, PDW and RDW compared to preoperative active disease phase and at postoperative 6 months versus preoperative values in patients achieving postoperative cure, and post-treatment versus pre-treatment GH, IGF-1, NLR, DNI, PDW and RDW values in patients without postoperative remission who received medical treatment. A reduction was also seen in post-treatment

versus pre-treatment MLR values but the difference was non-significant. Our findings suggest that surgical treatment and medical therapy can provide a reduction in inflammatory state in acromegalic patients. Chronic high levels of IGF-1 may result in an increase in inflammatory markers including NLR and this, in turn, may result in increased risk of atherosclerosis and cardiovascular disease. Early diagnosis and treatment are crucial in acromegaly because increases in subclinical inflammation associated with uncontrolled disease may be associated with high rates of morbidity and mortality.

Acromegaly can be regarded as an inflammatory disease both through direct effects of IGF-1 and GH and caused by inflammatory state associated with the condition. Additionally, inflammation can be suppressed by achieving cure with surgical treatment in particular as well as disease control through medical therapy. In this study, no significant relationships were observed between serum IGF-1 levels with inflammatory markers including NLR, RDW and PDW values in newly diagnosed patients with acromegaly. DNI, NLR, PDW and RDW can be considered as appropriate markers to assess inflammation in acromegaly. On the basis of these results, we believe that subclinical inflammation should be borne in mind in the management of acromegaly, since subclinical inflammation associated with uncontrolled IGF-1 levels may play an important role in increased morbidity and mortality. Further prospective, well-designed studies are warranted to corroborate these findings.

A number of limitations should be noted for the study. One limitation associated with the present study is that it had a retrospective design and was conducted at a single institution. Large, prospective and randomized clinical studies are needed to evaluate the clinical applicability of our findings. This study investigated subclinical inflammatory markers but not traditional inflammatory markers. Correlations between classic markers and novel inflammatory markers, DNI, NLR, MLR, PDW and RDW, were not analyzed.

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