

The Relationship Between Copeman Nodules and Disease Activation in Patients with Ankylosing Spondylitis Ankilozan Spondilitli Hastalarda Copeman Nodülleri ile Hastalık Aktivasyonu Arasındaki İlişki

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Summary

Objective: The diagnosis of ankylosing spondylitis is performed via blood tests, CRP, ESR, hemogram, HLA B27, radiologically, sacroiliac joint MR and physical examination methods. In this study, it was aimed to investigate Copeman nodules at the sacroiliac joint level in order to track disease activity in patients diagnosed with ankylosing spondylitis.

Material and Methods: Thirty-six ankylosing spondylitis patients who applied to Maltepe University Hospital Rheumatology outpatient clinic were included in the study. Subcutaneous Copeman nodules that were detected by palpation at the level of the sacroiliac joint have also been evaluated with ultrasonography. The BASDAI scores based on subjective complaints of patients have been calculated and recorded. CRP and ESR values, HLA B27 positivity results have been analyzed and sacroiliac MRI scans were examined.

Results: A total of 36 ankylosing spondylitis patients were included in this study. In terms of gender 44.4% of them were male (n=16), and 55.6% of them were female (n=20) with no significant difference. Mean BASDAI score of the cases was 4.1±2.3 and sedimentation rates were 14.9±13.1 mm/hour, CRP 18.1±3.3 mg/dL. Body mass indexes of 16 cases with Copeman nodules was 25.65±4.07 kg/m², sedimentation rate was 19.63±15.76 mm/h, CRP was 2.56±4.13mg/dL, BASDAI score was 4.4±1. The ultrasonography revealed that Copeman Nodules were of adipose tissue. Body mass indexes of 20 cases without Copeman Nodules were 23.92±3.94 k/m², sedimentation rate was 11.25±11.11 mm/h, CRP 1.29±1.58 mg/dL, BASDAI score was 3.9±2.7. Copeman nodule positivity was significantly correlated with BASDAI scores (p=0.009) and CRP (p=0.01), where no correlation existed with the sedimentation rate.

Conclusion: The high determination of BASDAI and CRP values in ankylosing spondylitis patients with nodules included in the study indicates that Copeman nodules may be associated with disease activation as a physical examination finding.

Key words: Ankylosing Spondylitis, Copeman Nodules, BASDAI Score, ESR, CRP

Özet

Amaç: Ankilozan spondilit tanısı kan testleri, CRP, ESR, hemogram, HLA B27, radyolojik, sakroiliak eklem MR ve fizik muayene yöntemleri ile konur. Bu çalışmada ankilozan spondilit tanılı hastalarda hastalık aktivitesini izlemek amacıyla sakroiliak eklem seviyesinde Copeman nodüllerinin araştırılması amaçlandı.

Gereç ve Yöntemler: Çalışmaya Maltepe Üniversitesi Hastanesi Romatoloji polikliniğine başvuran 36 ankilozan spondilit hastası dahil edildi. Ayrıca sakroiliak eklem seviyesinde palpasyonla saptanan cilt altı Copeman nodülleri de ultrasonografi ile değerlendirildi. Hastaların subjektif şikayetlerine dayalı BASDAI skorları hesaplandı ve kaydedildi. CRP ve ESR değerleri, HLA B27 pozitiflik sonuçları analiz edildi ve tüm hastaların sakroiliak MR görüntüleri incelendi.

Bulgular: Bu çalışmaya toplam 36 ankilozan spondilit hastası dahil edildi. Cinsiyete göre %44,4'ü erkek (n=16), %55,6'sı kadın (n=20) idi ve aralarında anlamlı bir fark yoktu. Olguların ortalama BASDAI skoru 4,1±2,3, sedimantasyon hızı 14,9±13,1 mm/saat, CRP 18,1±3,3 mg/dL idi. Copeman nodülü olan 16 olgunun vücut kitle indeksleri 25,65±4,07 kg/m², sedimantasyon hızı 19,63±15,76 mm/saat, CRP 2,56±4,13mg/dL, BASDAI skoru 4,4±1 idi. Ultrasonografide Copeman Nodüllerinin yağ dokusu olduğu ortaya çıktı. Copeman Nodülü olmayan 20 olgunun vücut kitle indeksleri 23,92±3,94 K/m², sedimantasyon hızı 11,25±11,11 mm/saat, CRP 1,29±1,58 mg/dL ve BASDAI skoru 3,9±2,7 idi. Copeman nodül pozitifliği, BASDAI skorları (p=0,009) ve CRP (p=0,01) ile anlamlı korelasyon gösterirken, sedimantasyon hızı ile korelasyon yoktu.

Sonuç: Çalışmaya dahil edilen nodüllü ankilozan spondilit hastalarında BASDAI ve CRP değerlerinin yüksek saptanması, Copeman nodüllerinin fizik muayene bulgusu olarak hastalık aktivasyonu ile ilişkili olabileceğini düşündürmektedir.

Anahtar kelimeler: Ankilozan Spondilit, Copeman Nodülleri, BASDAI Skoru, ESR, CRP

Kabul Tarihi: 17.Şubat.2023

Introduction

Ankylosing spondylitis (AS) is a complex, potentially debilitating disease with an insidious onset (1). The disease progresses to radiological sacroiliitis in several years thus leading to disability (2). Ankylosing spondylitis is one of the most interesting pathophysiological diseases of rheumatology and the main area of interest for the immune system with both autoimmune and autoinflammatory mechanisms. The rate of diagnosis of the disease is usually delayed 5-7 years with the current known diagnostic methods (1,3).

BASDAI (Bath Ankylosing Spondilitis Diseases Activity Index) scoring based on subjective questions, physical measurement methods, inflammatory markers and imaging methods are used to evaluate the activation of the disease (1,2,3,4). The pathogenesis of ankylosing spondylitis is still unknown. According to the available information, the disease first creates enthesitis in articular cartilage, ligaments and ligaments "insetsio" to the bone (5). The earliest finding is thought to be sacroiliitis. In the spine, anulus fibrosis and inflammatory granulation tissue develop in the intervertebral disc area. Then, this pathophysiological process progresses further, causing the development of "syndesmophytes" in the bone spreading throughout the entire spine, with a diagnostic "bamboo cane spine" appearance (1,6).

The diagnosis of AS is mostly made according to the physical examination of the patient, subjective complaints, CRP and sedimentation rate, HLA-B27 and MR imaging results from laboratory parameters (7). The first symptoms are mild pain in the sacral region, decreased physical activity with several hours of morning stiffness with the onset of a slowly developing disease. After a few months, the pain usually becomes continuous and bilateral. The patient wakes up and wanders from the aggravation of night pain (7). The other physical findings can be elaborated as loss of spinal mobility, anterior and lateral flexion, limitation in lumbar and thoracic extension. Enthesophyte formation is accepted as

a delayed finding of spondyloarthritis and chronic enthesitis (8,9). Direct radiography, sacroiliac MR and CT can be used as imaging methods for diagnosing AS. MR imaging is superior to other imaging methods (10).

According to all studies, Copeman nodules are considered as episacral lipoma and defined as a herniated subfacial adipose tissue due to a rupture in the thoracodorsal fascia. The thoracodorsal fascia is a deep fascia consisting of dense connective tissue with rich innervation covering the erector spina complex extending both in the thoracic and lumbar region of the trunk. In patients with a group of low back pain and Copeman Nodules, deep fascia consisting of this connective tissue has been investigated via USG (11). The examination results have indicated increased thickness and disorganization of these connective tissues (7,12). Generally, Copeman nodules are deep subcutaneous localized, rubbery, often mobile, round or oval shaped fat nodules (8,13).

All studies show Copeman nodules as one of the important causes of acute and chronic low back pain (9). Fat herniation usually occurs along the edge of the sacrospinalis muscle just above the posterior iliac crest. In these areas, subfacial fat pads herniate between the superficial and deep fascia and become inflamed by compression due to abnormal tension after trauma or hereditary weakness of the fascia (14). The mechanism of pain in the episacral lipoma is not fully understood but this may be due to the strangulation of the fat lobules that have herniated causing low back pain or the expansion of fat hernia within the inelastic hard fibrous capsule stretching the fibrous capsule, causing pain (15). Another explanation is attributed to the increased intranodular pressure. Copeman nodules can be seen in both genders but it is approximately three times more common in women, especially in moderately obese women (16,18)

In the presence of Copeman nodules patients describe very severe unilateral low back pain. This pain may also spread to the hips and legs

(16,19). At this stage whether Copeman nodules can be used as a determinant physical finding in evaluating AS activation might be evaluated by the clinician. In this study, we aimed to investigate Copeman nodules at the sacroiliac joint level, which is a physical examination finding that can be used to track disease activity in patients diagnosed with ankylosing spondylitis.

Material and Methods

The study protocol was approved by the Ethics Committee of Maltepe University Faculty of Medicine. (Date: 06.06.2018, number: 2018/900/46). Informed consents have been obtained from all the participants. 36 patients diagnosed with Ankylosing Spondylitis (AS) between the ages of 20 and 60 who applied to Maltepe University Medical Faculty Hospital Rheumatology Outpatient Clinic between 2016 and 2018 were included. Assessment of Spondylo-arthritis international Society (ASAS) criteria were accepted in the diagnosis of ankylosing spondylitis.

Inclusion criteria: Patients diagnosed with AS with findings that meet ASAS criteria and who have at least one joint with sacroiliitis in MR.

Exclusion criteria: Any health problem that can create an inflammatory formation in the pelvic region.

During the physical examinations of the AS patients, having the subcutaneous nodules detected at the level of the sacroiliac joint by palpation the patients with nodules have been further examined via USG imaging.

On physical examination, the nodules were palpated as round, mobile, semi-hard and oval. Texture and size of nodules were recorded. When the nodules were investigated with ultrasound, they were generally unilateral, round and in the form of fat herniation. At the same time, the sedimentation rate and CRP values of the patients were obtained at the time of admission, the BASDAI score was calculated, the presence of the HLA-B27 mutation and the sacroiliac joint MR information were recorded. Disease activation was evaluated.

IBM SPSS (Statistical Package for the Social Sciences) program were used to evaluate the

data. Firstly, the data are summarized with criteria and graphs, then non-parametric “Pearson Correlation Test” was utilized as an inner group comparison test in patients with and without nodules. The relationship analysis between categorical variables, statistical significance was examined with “Chi-Square Test” or “Fisher Exact Test”. In these comparisons, the difference between p values obtained by Pearson Correlation, Chi-square or Fisher Exact Tests greater than 0.05 was considered statistically insignificant.

Results

Of the 36 cases included in this study, 44.4% were male (n=16), 55.6% were female (n=20). There was no significant difference in terms of gender (p>0.05). The average age of the total study population was 42.19±7.41 years (34.87±8.51 years for females and 36.2±7.9 years males). There was no significant difference in age distribution by gender (p>0.05). The average body mass index of our patients was 24.80±4.00 kg/m². According to the MRI results, 69.4% (n=25) of the cases had bilateral sacroiliitis, and 66.7% (n=24) of were HLA B27 positive. Copeman nodule was positive in 44.5% (n=16) of the enrolled patients. The mean BASDAI score of the subjects was 4.1±2.3, the sedimentation rate was 14.9±13.1 mm/hour, and the CRP level was 18.1±3.3 mg/dL. Sacroileitis has been detected bilaterally in 25 patients (69.4%) and unilaterally in 11 patients (30.5%) (Table 1).

The average age of 16 cases with Copeman nodules was 44.4±8.6 years, body mass index 25.65±4.07 kg/m², sedimentation rate was 19.63±15.76 mm/hour and CRP 2.56±4.13 mg/dL. BASDAI score was found as 4.4±1.9 and the HLA-B27 positivity has been observed in 56.3% (n=9) of these cases while 43.7% (n=7) of them were negative (Table 2).

The average age of 20 cases without Copeman nodules was 40.4±5.8 years. Body mass index was 23.92±3.94 Kg/m², sedimentation rate 11.25±11.11 mm/hour and CRP was 1.29±1.58 mg/dl. BASDAI score was observed as 3.9±2.7 and the HLA-B27 positivity has been observed in 75% (n=15) of these cases while 25% (n=5) (Table 2) of them were negative.

Table 1. Demographic and laboratory information of the cases belonging to the study group

	Age (year)	Gender	Body Mass Index (BMI)	MR (Bilateral Sacroiliitis)	HLA-B27 Positivity	Copeman Nodules	BASDAI	ESR (mm/h)	CRP (mg/dL)
N	36	F:20 M:16	36	25 / 36	24 / 36	16/36	36	36	36
Main / percent	42,19±7,41 Female: 34,87±8,5 Male: 36,2±7,9	Female: %55,6 Male: %44,4	24,80±4,00	%69,4	%66,7	%44,5	4,13±2,37	14,97±13,83	1,8±3,01*

* CRP value distributions of cases are in a wide range Maximum: 13mg/dL, Minimum: 0,4mg/dL

In patients with Copeman nodules, a significant correlation was found with BASDAI scores (p=0.009) and CRP (p=0.01), regardless of age and gender, while no correlation was found with the sedimentation rate (p=0.56) (Table 2).

Table 2. Subgroup examinations of the cases included in the study

Group Parameters	Copeman Nodules	Results
Age (years)	Yes	44,44±8,67
	No	40,40±5,84
Body Mass Index (Kg/m ²)	Yes	25,65±4,07
	No	23,92±3,94
BASDAI	Yes	4,41±1,91
	No	3,91±2,71
Sedimentation Rate (mm/h)	Yes	19,63±15,76
	No	11,25±11,11
CRP (mg/dL)	Yes	2,56±4,13
	No	1,29±1,58
HLA-B27	Yes	9/16 (%56,3)
	No	15/20 (%75,0)

The relationship between nodule presence and HLA B27 was not statistically significant (p=0.203). HLA B27 positivity and negativity rates were similar in patients with nodule positive and negative (p=0.20). There was no difference between the group with and without the Copeman nodule in terms of body mass index (p=0.09). Another finding that we could not detect statistically but evaluated in our patients was the sensitivity of the patient when the pressure on the Copeman nodule was applied in patients with persistent pain.

When these Copeman nodules in patients were displayed ultrasonographically, sonographic features that were generally close to the same sonographic features as the adipose tissue has

been found, and it was observed to have similar features compared to MRI images (Figure 1).

Figure 1. Ultrasonographic views of Copeman Nodules



Discussion

The existence of Copeman nodules, suggests that mechanical and inflammatory mechanisms occur in these patients as an intersection point in patients with ankylosing spondylitis (19). According to previous studies, Copeman nodules were categorized as episacral and thoracodorsal lipomas that herniated from subfascial adipose. Thoracodorsal fascia has rich innervation covering the extending erector spinae complex with trunk dense connective tissue (20). Copeman nodules can be observed in both sexes but obesity has been accepted as the predisposing factor of mechanical spinal problems (20,21). However, relationship between Copeman Nodules and Body Mass Index was not found in this study population.

In previous research many studies have been conducted on inflammatory markers and their correlation with disease activity. Vries et al. (2009) administered etanercept to 155 ankylosing spondylitis patients and examined the change in

their inflammatory markers (22). At the end of 3 months ESR and CRP decrease were significantly associated with the improvement of BASDAI scores compared to baseline. They found that the correlation of with ESR was the strongest with regards to BASDAI scores. Elevated baseline CRP and levels have revealed the highest predictive value for response (22). In the current study, no relationship between sedimentation rate and Copeman nodules was detected but significant correlation between BASDAI score and CRP was found. In a study conducted by Wagner et al. In patients receiving Infliximab treatment, a correlation was found between CRP value and BASDAI score (17). Compared to patients with a BASDAI score of >4, patients with a BASDAI score of <4 had a higher CRP value in those with a BASDAI score of >4. On the other hand, Liu et al. (2005) conducted a study to determine whether erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) is more appropriate in measuring the disease activity in ankylosing spondylitis (AS) and found that neither ESR nor CRP was superior for assessing disease activity (23). Vries et al. (2009) have also stated that the normal baseline levels of CRP were significantly associated with nonresponse (22).

One of the important tools used in the diagnosis of AS disease is BASDAI scoring. It is a questionnaire that can be applied in BASDAI polyclinic, which is evaluated with a simple and fast questioning and includes all clinical complaints of the disease. CRP and sedimentation rate are the most used parameters among the laboratory values used to show the activation of the disease (24). The BASDAI scale includes patient-reported assessments and has been extensively used in a majority of clinical trials up to date (25). There are also several other scales such as ASDAS which also includes laboratory parameters (25,26,27,28). Nevertheless, by adding ESR, CRP into this study we wanted to elaborate the BASDAI (patient reported assessment) association with ESR, CRP in Copeman nodules positive patients to interpret their disease activity or progression. In this study, the high determination of BASDAI and CRP values in patients with nodules should suggest that the presence of nodules may be related to disease activation.

Copeman nodules cause severe chronic back pain for the patient and as thoracodorsal fascia has

rich innervation covering the extending erector spinae complex with trunk dense connective tissue the pain load could cause a high burden for the patient. In patients with Copeman nodules, a significant correlation was found with BASDAI scores ($p=0.009$) and CRP ($p=0.01$), regardless of age and gender. This study reveals the relationship between CRP and BASDAI, which are globally considered as indicators of inflammatory factors may have an association with Copeman nodules. These nodules have more connective tissue character with ultrasonographic and MRI images (29,30). As a result of these findings, we think that Copeman Nodules can be used in the follow-up of the inflammatory process at the tissue level of patients with AS with the studies to be conducted with high number of cases.

Conclusion

The high determination of BASDAI and CRP values in ankylosing spondylitis patients with nodules included in this study indicates that Copeman nodules may be associated with disease activation as a physical examination finding.

Funding

There is no specific funding related to this research.

Editorial Support

The editorial support of this article has been conducted by QA Executive Consultancy, Ozan Batigun MD, MBA in 2021.
www.QAexecutiveconsultancy.com

Competing interests

The authors declare that they have no competing interests.

Informed consent

Informed consent has been obtained from all the patients before the initiation of the study.

Institutional Review Board Approval

The ethics committee approval date 2018 and protocole number: 192.

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