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Original Article

Computed tomography and magnetic resonance imaging features for differentiating functioning from non-functioning adrenal lesions

Derya Koseoglu[1], Mazhar Muslum Tuna[2], Narin Nasiroglu Imga[3], Bercem Aycicek[4], Mehtap Navdar Basaran[5], Cagdas Senel[6], Altug Tuncel[7], Dilek Berker[3], Serdar Guler[8]

[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Hitit University, Corum, Turkey
[2]Department of Endocrinology and Metabolism, Umraniye Education and Research Hospital, Istanbul, Turkey
[3]Department of Endocrinology and Metabolism, Saglik Bilimleri University, Ankara City Hospital, Ankara, Turkey
[4]Department of Endocrinology and Metabolism, Gazi Yasargil Education and Research Hospital, Diyarbakır, Turkey
[5]Department of Endocrinology and Metabolism, Kanuni Sultan Suleyman Education and Research Hospital, Istanbul, Turkey
[6]Department of Urology, Faculty of Medicine, Balikesir University, Balikesir, Turkey
[7]Department of Urology, Saglik Bilimleri University, Ankara City Hospital, Ankara, Turkey
[8]Department of Endocrinology and Metabolism, Ankara Liv Hospital, Ankara, Turkey

Abstract

Aim: It is not well known whether the radiological features of adenomas differ between functioning and non-functioning adrenal lesions (NFAL). The aim of this study was to evaluate the characteristic features of computed tomography (CT) and magnetic resonance imaging (MRI) characteristics among functioning and non-functioning adrenal lesions.

Material and Methods: This retrospective study included 89 patients with functioning adrenal lesions and 148 patients with NFAL, whose CT or MRI findings were present. Group 1 included patients with functioning adrenal lesions and group 2 patients with NFAL.

Results: In patients with functioning adrenal mass, adenoma size (p:0.001), unenhanced and early-enhanced Hounsfield units (HU) (p<0.001) were significantly higher compared to those with NFAL. Among the patients with functioning adrenal mass; Cushing's syndrome, pheochromocytoma and primary hyperaldosteronism were diagnosed in 34, 32 and 23 patients, respectively. Mean early-enhanced HU was higher in all functioning groups compared to NFAL (p<0.001, all). ROC analysis showed 80% specificity and 82.7% sensitivity for determining functioning adrenal masses with an early-enhanced CT attenuation value of 27 HU. On T1-weighted images functioning adrenal lesions were more commonly hypointense than NFAL (p=0.02).

Conclusion: This study reveals that functioning adrenal lesions might be differentiating from NFAL using CT features. Especially early-enhanced CT attenuation, which is elevated in all functioning adrenal mass forms, may be used effectively for this purpose.

Keywords: Adrenal incidentaloma; computerized tomography; cushing's syndrome; pheochromocytoma; primary hyperaldosteronism

INTRODUCTION

Adrenal incidentalomas (AIs) are adrenal lesions greater than 1 cm which are detected during abdominal imaging procedures that had been performed for any reason (1). The prevalence of AIs is about 6% in autopsy studies and about 4% using high-resolution computed tomography (CT) or magnetic resonance imaging (MRI), but a prevalence of around 1% was reported in routine clinical practice (1,2). Most of these lesions are benign and non-functioning, but appropriate imaging procedures and hormonal evaluation should be performed, to find out malignancy and functioning adrenal lesions (3, 4). CT features are effective in determining malignancy in adrenal lesions (3). The functioning adrenal lesions are Cushing's syndrome (CS), pheochromocytoma (PHEO) and primary hyperaldosteronism (PH), respectively according to incidence (4). According to the American Association of Clinical Endocrinologists (AACE) guidelines, functional studies including overnight dexamethasone (DXM) suppression test to rule out CS, plasma aldosterone to plasma renin activity ratio to rule out PH particularly for hypertensive patients, and a 24-hour urinary fractionated metanephrines or plasma fractionated metanephrines to

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Corresponding Author: Derya Koseoglu, Department of Endocrinology and Metabolism, Faculty of Medicine, Hitit University, Corum, Turkey **E-mail:** drderyaksgl@gmail.com

rule out PHEO, are essential to determine the functional status. Routine testing for androgen excess is not recommended (4). Non-invasive imaging procedures are being used to determine the nature of adrenal lesions. However, it is not well known whether the radiological features of adenomas are different between functioning and non-functioning adrenal masses. The aim of this study was to assess the characteristic imaging features of functioning and non-functioning adrenal lesions (NFAL) regarding to imaging procedures and to determine the low-risk patients based on functioning status to prevent further evaluation.

MATERIALS and METHODS

Patient Recruitment

We retrospectively reviewed the medical records of patients who were followed due to a functioning or non-functioning adrenal mass at Ankara Numune Education and Research Hospital. Of these patients, patients with unavailable CT or MRI and patients with known adrenocortical carcinoma were excluded from the study. The remaining 89 patients were included in the study as the case group, which contained 34 patients with CS, 32 with PHEO and 23 with PH. Of these patients 77 patients underwent adrenalectomy and the laboratory evaluations were normalized after the removal of the tumor in all cases. The remaining 12 patients (4 were diagnosed as Subclinical CS and 8 as PH) were followed without surgery. As the control group, patients who were diagnosed with NFAL and had available CT or MRI were enrolled in the study (n=148, group 2). The diagnosis of AI was determined as the detection of an adrenal lesion more than 1 cm of size on abdominal imaging performed for reasons other than suspected adrenal diseases (5). Patients with known malignancy and those with adrenal lesions suspected of malignancy on CT or MRI were not included in the analysis, because malignancy evaluation was out of the scope of this study. Also, patients with bilateral adrenal mass lesions were not recruited in analysis to obtain a homogenous study group. Patients who had a lesion greater than 4 cm were included in the study only if their pathology results proved that the lesion was a benign adenoma after surgery.

All patients with AIs underwent the following tests: Serum morning cortisol and adrenocorticotropin hormone (ACTH) levels were determined under basal conditions. All patients had undergone an overnight 1 mg DXM suppression test. The suppression was adequate when morning cortisol was below 1.8 mcg/dL (6). If morning cortisol levels were not suppressed, a two-day low-dose DXM suppression test was done. For DXM suppression test 0.5 mg DXM was given four times a day (2 mg a day) for two days. After DXM suppression test, morning cortisol value less than 1.8 mcg/dL was considered as normal. If suppression was not achieved further tests were performed according to AACE guidelines. All control subjects had normal levels of urinary metanephrine and normetanephrine excretion. Measurements of the ratio of plasma aldosterone concentration (ng/dL) to plasma renin activity (ng/mL/hour), was performed in patients who had hypertension, and a plasma aldosterone/ renin activity ratio below 20 was considered normal. All patients with AIs were managed for diagnosis, treatment, and follow-up according to AACE guidelines recommendations (4). Data collected for patients were sex, age, and hormonal tests, diameter of the adrenal lesion, and the radiological imaging features of the lesion. The local ethics committee of Ankara Numune Education and Research Hospital approved the present study.

Radiologic Imaging

The CT and MRI, which detected a new adrenal lesion, were used in this study. If more than CT and MRI were available only the first imaging method was included in the statistical analysis. The CT examinations were performed using a multidetector-row helical CT scanner (Somatom Sensation 16; Siemens Medical Systems, Erlangen, Germany) or a dual-detector-row helical CT scanner (Somatom Emotion Duo/Emotion 6; Siemens Medical Systems, Erlangen, Germany). CT examinations were performed as described below: 10-mm collimation and 5-mm reconstructed section thickness for dual-detector-row CT scanner; 5-mm collimation and 5-mm section thickness for multidetector-row CT scanner. In initial management, an unenhanced adrenal image was obtained. If the unenhanced CT attenuation value of the adenoma was more than 10 Hounsfield units (HU), post-contrast images were obtained at 1 min (early-enhanced) and 15 min (delayed-enhanced) to allow calculation of a washout percentage. The percentage of "absolute washout" was calculated by the formula: [P-R/P-S] × 100. P is the value of enhancement at 60—90 seconds (assumed peak enhancement), R is the delayed-enhancement value 10 or 15 minutes after contrast injection, and S is the unenhanced density measured without injection. A 60% reduction in absolute washout allows the diagnosis of adenoma with a specificity of 100% (7).

MRI studies were performed with a 1.5 Tesla superconducting magnet scanner (Signa; GE Healthcare, Milwaukee, Wisc., USA). A spin echo technique was used to obtain 5 mm contiguous three-dimensional sections of the upper abdomen. T1-weighted and T2-weighted images were obtained. MRI studies were also integrated using T1 chemical-shift imaging.

Statistical Analysis

For statistical analysis SPSS (Statistical Package for the Social Sciences) 18.0 was used. One sample Kolmogorov-Smirnov test was used to evaluate the normality of continuous data. Normally and non-normally distributed continuous data are presented as mean±standard deviation and median (minimum-maximum), respectively. The groups were compared with independent samples Student's t-test and Mann-Whitney U test for normally and non-normally distributed data, respectively. Statistical analysis was performed using One-way ANOVA and Tukey post hoc tests for multiple comparisons where appropriate with significance accepted at $p<0.05$. Categorical variables are presented as number of cases (percentage) and were compared between groups with Pearson's Chi-Square test.

Receiver-operating characteristic (ROC) curve analysis was performed to specify optimal cut-off value of the radiological parameters for predicting functioning adrenal masses. p values <0.05 was considered statistically significant.

RESULTS

The study population consisted of 89 patients with functioning adrenal lesions (group 1) and 148 patients with NFAL (group 2). Of the patients, 164 were female and 73 were male, and no significant difference was present between groups according gender. The mean age of the participants was 53.53 ± 11.86 years, and patients in group 2 were statistically significantly older (55.36 ± 10.67 and 50.51±13.15, respectively). NFAL were mostly seen in the left adrenal, and functioning adrenal tumor in the right adrenal, but the difference was not statistically significant (Table 1). The antero-posterior and transverse adenoma diameters were both statistically significantly greater in group 1 than in group 2 (Table 1). 169 patients had available CT, 98 had MRI and 30 patients had both CT and MRI. Consequently 169 CT (64 in group 1 and 105 in group 2) and 98 MRI (45 in group 1 and 53 in group 2) findings were included for statistical analysis. On CT, the unenhanced and early-enhanced attenuation values were significantly higher in patients with functioning adrenal masses compared to NFAL, whereas delayed-enhanced attenuation values and the absolute wash out-ratios were not statistically different (Table 2).

Table 1. Demographic characteristics of participants

	Group 1 (N=89)	Group 2 (N=148)	p value
Age	50.51 ± 13.15	55.36 ± 10.67	**0.004**
Gender (F/M)	66/23	98/50	0.25
Localisation (R/L)	48/41	68/80	0.28
Adenoma size (A-P)¶	31.53 ± 18.21	24.20 ± 14.77	**0.002**
Adenoma size (transverse)¶	26.09 ± 16.88	19.01 ± 12.11	**0.001**

F: female, M:male, R: right, L: Left, A-P: antero-posterior
¶ The size were measured with CT, but when CT was not available MRI was used

In group 1, 34 (38%) patients had CS, 32 (36%) had PHEO and 23 (26%) patients had PH. Among these patients CT attenuation values were available in 23, 20 and 21 patients, respectively. Patients with PHEO had higher unenhanced CT attenuation values, larger adenoma size and lower absolute wash-out ratio, as compared to CS, PH and NHAL (Tables 3 and 4). Respectively 91 (86.7%), 20 (87%), 3 (15%) and 19 (90.5%) of the patients had unenhanced CT attenuation value lower than 20 HU in NFAL, CS, PHEO and PH, (all p-values <0.001 between PHEO and the other subgroups) (Table 3). Early-enhanced attenuation value was significantly lower in NFAL patients than the other three subgroups (p:<0.01) (Table 4). Delayed-enhanced attenuation value was higher in the PHEO subgroup, which was statistically significant as compared to NFAL (P<0.01) (Table 4). ROC curve analysis found a cut-off value of 27 HU on early-enhanced attenuation for detecting functioning adrenal mass with a specificity of 80% and sensitivity of 82.7% on (Figure 1) [(AUC:0.85, (95% CI 0.75-0.95)].

Table 2. Comparison of groups according to characteristic features on CT

	Functioning adrenal lesions (N=64)	Non-functioning adrenal lesions (N=105)	p value
Unenhanced CT attenuation values (HU)	11.87 ± 24.14	-1.50 ± 18.00	**<0.001**
Early –enhanced CT attenuation values (HU)	45.55 ± 23.09	17.88 ± 19.34	**<0.001**
Delay -enhanced CT attenuation values (HU)	28.89 ± 25.82	17.07 ± 26.36	0.059
Absolute wash-out ratio (%)	53.65 ± 17.86	58.63± 20.88	0.253

Table 3. Distribution of clinical diagnosis by precontrast CT attenuation values

	N	<20 HU (N, %)	≥20 HU (N, %)
Non functioning adenoma	105	91 (86.7)	14 (13.3)
Cushing's syndrome	23	20 (87.0)	3(13)
Pheochromocytoma	20	3 (15)	17 (85)*
Conn's syndrome	21	19 (90.5)	2 (9.5)

*P<0.001; HU: Hounsfield units

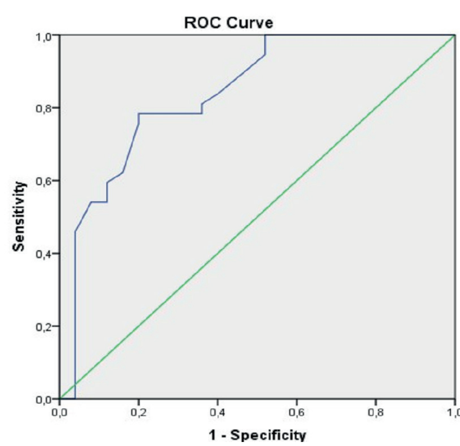

Figure 1. ROC curve analysis with early enhanced HU for detecting functioning adrenal mass

Because the specific radiological pattern of PHEO is well-known, the statistical analysis was also performed without patients with PHEO. The only statistically significantly different radiological value was early-enhanced attenuation value that was lower among the NFAL group compared to patients with CS and PH (17.88±19.30 and

41.70± 20.99, respectively). ROC curve analysis was performed without patients with PHEO and the value of 27 HU had a specificity of 78.4% and sensitivity of 80% to discriminate CS and PH from NFAL [(AUC:0.84, (95% CI 0.73-0.94)].

Among functioning adrenal lesions 44.4% were hypointense on T1-weighted MRI images, versus 18.9% of the NFAL (p=0.024). This significance was mainly due to PHEO, because up to 77.8% of the lesions in this subgroup were hypointense on T1-weighted MRI images. When PHEO patients were excluded from this analysis, only 22.2% of the functioning lesions were T1 hypointense, which was not significantly different from NFAL. T2-weighted images and chemical shift properties between functioning and NFAL were not significantly different (Table 5).

Table 4. Comparison of CT features according to clinical diagnosis

	NFAL (N=105)	CS (N=23)	PHEO (N= 20)	PH (N=21)	p value
Adenoma size (A-P)	23.36 ± 11.94	29.52 ± 11.26	37.70 ± 20.60	19.81 ±7.05	<0.001*
Adenoma size (transverse)	17.69 ± 8.03	24.43 ± 11.25	32.75 ± 18.37	15.05 ± 6.34	<0.001*
					0.038**
Unenhanced CT attenuation (HU)	-1.50 ± 18.00	2.48 ± 16.55	35.30 ± 21.90	-1.26 ± 16.34	0.001***
Early enhanced CT attenuation (HU)	17.07 ± 26.36	41.68 ± 20.75	53.40 ± 26.45	41.72 ± 21.85	<0.01****
Delay enhanced CT attenuation (HU)	17.07 ± 26.36	23.78 ± 19.03	42.00 ± 30.74	19.71 ± 21.23	0.013*****
Absolute wash-out ratio (%)	58.63 ±20.88	59.70 ± 14.58	38.33 ± 12.97	61.16 ± 15.58	<0.01***

* p-value between PHEO and NFAL and PH, ** p-value between PHEO and CS, *** p-value between PHEO and other three groups, **** p-value between NFAL and other three groups; ***** p-value between NFAL and PHEO
NFAL: Non functioning adenoma; CS: Cushing's syndrome; PHEO: Pheochromocytoma; PH: Primary hyperaldosteronism; A-P: Antero-posterior, HU: Hounsfield units

Table 5. Comparison of groups regarding the features on Magnetic resonance imaging

	NFAL (N=53)	CS (N=16)	PHEO (N=18)	PH (N= 11)
T1 weighted image				
hypointense, %	18.9	37.5	77.8	0
isointense, %	71.7	50	16.7	100
hyperintense, %	9.4	12.5	5.6	0
T2 weighted image				
hypointense, %	11.3	12.5	17.6	0
isointense, %	62.3	68.8	17.6	100
hyperintense, %	26.4	18.8	64.7	0
Decreased signal intensity out-of-phase, %	74.5	72.2	20	100

NFAL: Non functioning adenoma; CS: Cushing's syndrome; PHEO: Pheochromocytoma; PH: Primary hyperaldosteronism

DISCUSSION

Our study investigated retrospectively CT and MRI features of NFAL and functioning adrenal lesions, and revealed that CT and T1-weighted MRI characteristics can help to distinguish lesions according to their functioning status. Among the patients with functioning adrenal mass; Cushing's syndrome, pheochromocytoma and primary hyperaldosteronism were diagnosed in 34, 32 and 23 patients, respectively. Especially early-enhanced HU, which is significantly elevated in all functioning adrenal lesions (p<0.001), may be used effectively to differentiate functioning adrenal lesions from NFAL with relatively high values of specificity and sensitivity, even after removing PHEO patients from the analysis. ROC analysis showed 80% specificity and 82.7% sensitivity for determining functioning adrenal masses with an early-enhanced CT attenuation value of 27 HU. On T1-weighted images functioning adrenal lesions were more commonly hypointense than NFAL (p=0.02).

AI has been rapidly increasing since the use of cross-sectional imaging increases with a large impact on health care costs (8). Although the most of the adrenal masses are nonfunctional and benign, they may cause important clinical problems due to hormonal hyperfunction and malignancy risk. While most AIs are nonfunctional, 10 to 15% secrete excessive amounts of hormones (5, 9). The most complete analysis of this issue comes from a review of all 828 published articles on AIs from 1980 to 2008 (9). Primary adrenal carcinoma was found in 1.9% and metastases in 0.7%, whereas the remaining lesions were benign. In this meta-analysis NFAL was detected in 89.9% patients of all cases, whereas the percent ratios for CS, PHEO and PH were 6.4%, 3.1% and 0.6% respectively (9).

In a study from Korea, age and location were not statistically significant factors for detecting functioning adrenal mass (10), but our study showed significantly higher mean age in NFAL patients. Location of the tumor was not associated with functioning lesions. In our study, most of the patients were female in both groups and there was no significant difference regarding gender between groups. The risk of functioning adrenal tumors seemed to be higher in adenomas larger than 3 cm, but this finding has not been confirmed by others (11-13). Similarly in our study, patients with functioning adrenal mass had a larger size of lesion than those with NFAL. But in subgroup analysis only PHEO lesions were significantly larger than NFAL. The discrepancy between this studies may be due to a selection bias, because we did not recruit patients with a lesion greater than 4 cm as control group, unless surgically resected and found to be benign.

The radiological characteristics of PHEO are well known. An unenhanced CT attenuation of less than 10 HU is rarely seen in PHEO (14, 15). A study by Sane et al. supported this knowledge in which they had 146 non-functional AIs that had an unenhanced CT attenuation value <10 HU (16). Reginelli et al. found in their study that two of four cases with CS, three of six cases with PH and one of two cases with PHEO had an unenhanced CT attenuation value <10 HU (17). In another study, female gender and an unenhanced CT attenuation value >10 HU were independent risk factors for functional AIs (10). In a published study conducted on 318 patients with AI, attenuation values of HU <10, 10-20 and >20 were respectively 45%, 30%, and 25% for nonfunctioning adrenal adenomas (n= 238); 60%, 20%, and 20% for CS (n=20); 64%, 14%, and 22% for aldosteronoma (n=14); and 4%, 12%, and 84% for PHEO (n=23) (18), which is consistent with our findings. Another study reported that unenhanced and enhanced CT attenuation in NFAL was significantly lower than PHEO (p<0.01) (19). It is suggested that routine biochemical screening for PHEO in homogenous adrenal adenomas with an unenhanced CT attenuation below 10 HU is not necessary (15, 20). Our study confirmed higher unenhanced attenuation values in functioning adrenal mass group. When subgroup analysis was performed, attenuation was significantly higher among patients with PHEO, but the other functioning masses (CS and PH) had similar unenhanced CT attenuation values with NFAL, which is similar to another recent study (21).

Most PHEOs show slow wash-out values (4, 22), but around 25% of patients with PHEO have higher wash-out ratio and can mimic wash-out patterns similar to NFAL (23). The wash-out pattern of CS and PH are not well validated to date. Similar to the previous literature, our study showed low wash-out values in patients with PHEO compared to NFAL. Furthermore the wash-out value was also lower compared to CS and PH, and because of this reason when functioning adrenal mass was compared with NFAL there was no difference in wash-out ratio between groups. According to these findings we can say that wash-out cannot be used to differentiate functioning adrenal masses from NFAL, but can be used as an indicator for predicting PHEO.

Early-enhanced CT attenuation value was higher in functioning adrenal mass group compared with NFAL. In the subgroup analysis CS, PHEO and PH had all higher early-enhanced CT attenuation value compared with NFAL (p<0.001). A cut-off value of 27 HU was calculated to differentiate adrenal lesions according to functioning status, with >80% specificity and sensitivity. Similar findings were detected when patients with PHEO were excluded from the analysis. To the best of our knowledge, a similar finding showing effective use of early-enhanced CT attenuation values in differentiating functioning adrenal masses from non-functioning masses has not been previously reported in the literature. Because unenhanced CT attenuation value and wash-out ratio were not different between CS, PH and NFAL, early-enhanced CT attenuation value is more effective than unenhanced CT attenuation value and washout patterns in predicting functional adrenal mass.

T2 signal hyper-intensity and significant persistent gadolinium enhancement were both specific for PHEO, but may not be present in up to 25–30% of cases (24, 25). But this may depend on the criteria used to describe hyperintensity (26). MRI signal intensity ratios were not found to effectively differentiate hyperfunctioning and non-hyperfunctioning adenomas in a recently published study (27). In our study, on T1-weighted hypointensity was seen more commonly in functioning adrenal lesions as compared to NFAL. Most of the lesions which were hypointense were PHEO, and because of this MRI findings were compared after the exclusion of PHEO patients. With this modification we found that NFAL had a similar appearance with CS and PH. Similar to the aforementioned study (27). Other MRI features were similar among adenoma's types. Thus our findings suggest that MRI signal reflect tumor tissue composition rather than endocrine function. But if a lesion is hypointense on T1-weighted images PHEO should be suspected.

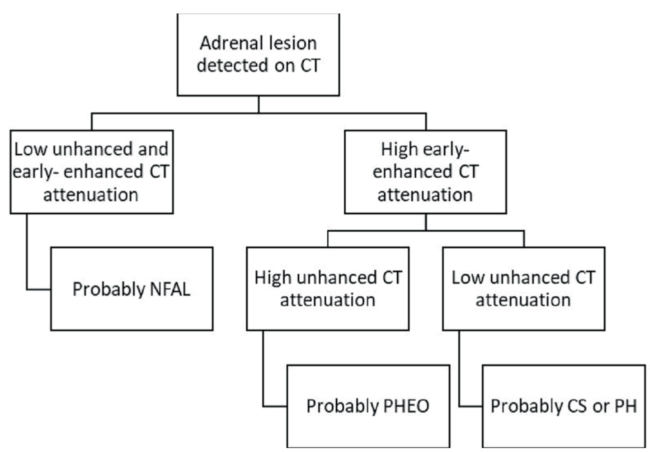

Figure 2. Our recommendations for the differential diagnosis of adrenal lesions

CONCLUSION

This study showed that functioning adrenal lesions may be distinguished from NFAL by using CT imaging features. Especially early- enhanced CT attenuation value was the most effective parameter in determining functional adrenal lesions with high specificity and sensitivity. We may thus recommend performing CT imaging to predict NFAL in newly detected adrenal lesions, which has been detected on MRI. If the lesion has low unenhanced and early- enhanced CT attenuation, it is probably a NFAL. Lesions with high early-enhanced CT attenuation are probably functioning lesion. Such lesions should be evaluated for unenhanced CT attenuation, and lesions with high unenhanced CT attenuation are probably PHEO and lesions with low unenhanced CT attenuation are probably CS or PH (Figure 2). But this recommendation should be reinforced by further studies.

Competing Interests: The authors declare that they have no competing interest.

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Ethical Approval: The present study was approved by the local ethics committee of Ankara Numune Education and Research Hospital (No:E-15-400).

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