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# Clinical and Pathological Features of Adrenal Myelolipoma and Myelolipomatous Metaplasia Cases in Our Hospital Over 13 Years

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## Abstract

**BACKGROUND/AIMS:** The development and widespread use of abdominal imaging techniques has increased the incidence of unexpected adrenal tumors called adrenal incidentaloma. Adrenal myelolipomas are the second most common incidentalomas. Similar myelolipomatous morphology appears as a secondary degenerative change in other adrenal lesions and is called myelolipomatous metaplasia. This study investigated the adrenal entities of the last 13 years which had myelolipomatous components.

**MATERIALS AND METHODS:** In this retrospective observational study, cases diagnosed as adrenal myelolipoma or myelolipomatous metaplasia between January, 2009 and January, 2022 were re-examined regarding their age, gender, localization, lesion size, and secondary histopathological changes, accompanying pathological diagnoses as well as clinical and radiological data.

**RESULTS:** Eleven adrenal myelolipoma cases and 6 myelolipomatous metaplasia cases were detected. In myelolipomas, the mean age was 55.45 years, 73% were female and 82% were located on the right side. The lesions were encapsulated and their mean size was 7 cm. One case had a diagnosis of subclinical Cushing's syndrome and the others were hormonally inactive. Some cases were accompanied with hypertension (27%), type 2 diabetes (18%), and asthma (18%). All myelolipomatous metaplasias, which are non-encapsulated, were detected in adrenocortical adenomas. The mean age was 58 years; nonencapsulated and 67% were located on the right side with no gender predilection. Concomitant hypertension (50%), diabetes /33%, and asthma (33%) were frequent.

**CONCLUSION:** Adrenal myelolipoma and myelolipomatous metaplasia both contain adipose and myeloid components. Myelolipoma is a benign and encapsulated neoplasia which is usually detected incidentally. They frequently coexist with chronic diseases such as hypertension, diabetes and asthma.

**Keywords:** Adrenal, myelolipoma, myelolipomatous metaplasia

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## INTRODUCTION

The development and widespread use of abdominal imaging techniques have increased the incidence of unexpected adrenal tumors called adrenal incidentaloma.[1,2] These cases, with a reported incidence of 10-15% today, are mostly biochemically nonfunctional, small, and benign. However, since one in ten cases can be functional or show malignancy, their detection and pathological diagnosis are important.[3-5] Adrenocortical adenomas constitute the majority (60-70%), while adrenal myelolipomas are the second most common adrenal incidentalomas (6-16%).[6-9]

Adrenal myelolipoma is a benign neoplasm composed of hemopoietic and adipose tissues.[9] Similar myelolipomatous morphology appears as a secondary degenerative change in other adrenal neoplastic and non-neoplastic entities, especially in adrenocortical adenoma, and is called myelolipomatous metaplasia.[10] Lipomatous tumors are rare among adrenal tumors. Although myelolipoma is the most common tumor in this group, a differential diagnosis should be made with myelolipomatous changes in lipomas, teratomas, angiomyolipomas, and adrenocortical lesions.

Myelolipoma was first described by Giercke in 1905 and named by Oberling in 1929.[5,11] The 2017 classification by the World Health Organization (WHO) included myelolipoma in the category of mesenchymal and stromal tumors of the adrenal cortex, with its current clinical and pathological details.[7] The 2022 World Health Organization bluebook covers a new separate chapter on myelolipoma.[12] According to one of the hypotheses on the origin of myelolipoma, it is thought that cancer, Cushing's disease, hypertension, diabetes, obesity, and/or stressful life conditions lead to necrosis or inflammation in the adrenal cortex tissue, causing prolonged endogenous adrenocorticotropic hormone stimulation and chronic adrenal stimulation. As a result, metaplasia may occur in reticuloendothelial cells, leading to the formation of adrenal myelolipoma.[1,7,13] According to another hypothesis, adipocytes develop from mesenchymal stem cells in the vessel walls in the stromal adipose tissue of the adrenal cortex under the influence of various stimuli. As they differentiate, these adipocytes become inflammatory, stimulating the adrenal cortex to release substances which recruit hematopoietic progenitors to the environment.[6] These also seem to be responsible for the development of myelolipomatous metaplasia.[10]

In this study, which was conducted with our data of the last 13 years, incidental entities of the adrenal gland which are adrenal myelolipoma with adipose and hematopoietic components and adrenocortical adenoma with myelolipomatous metaplasia were reviewed and discussed in the light of findings in the literature.

## MATERIALS AND METHODS

Cases reported as adrenal myelolipoma and myelolipomatous metaplasia between January, 2009 and January, 2022 in the University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Medical Pathology were included in this retrospective observational study. Paraffin blocks, hematoxylin-eosin-stained slides, pathology reports, laboratory data, and patient files were extracted from the archive and re-examined. Data regarding these cases such as age, gender, location, lesion size and secondary histopathological changes, pathological, clinical, and radiological diagnoses were recorded. For statistical analysis, using GraphPad Prism 8.0.1, descriptive data analysis (mean and percentage values) was performed for quantitative data and Independent t-test and chi-squared test were used for comparisons. A value of $p<0.05$ was considered statistically significant.

**Ethics Committee Approval:** University of Health Sciences Türkiye, Kartal Dr. Lütfi Kirdar City Hospital Clinical Research Ethical Committee (approval number: 2022/514/220/13, date: 22.02.2022).

### Statistical Analysis

Statistical analysis between myelolipoma and myelolipomatous metaplasia cases did not reveal any statistically significant relationship between gender, age, or the location of the lesions ($p>0.05$).

## RESULTS

### Myelolipoma

Eleven cases diagnosed as adrenal myelolipoma and 6 cases of myelolipomatous metaplasia were included in this study. Adrenal myelolipoma cases were between 31 and 72 years old (mean: 55.45); 8 cases (72.7%) were female, and 3 cases (27.3%) were male; 9 of the cases (81.8%) were located in the right and 2 (18.2%) in the left adrenal; macroscopically, the cases were round or elliptical and encapsulated, with their sizes ranging from 0.6 cm to 11.5 cm (mean: 7.18 cm). There were yellow and red-brown areas in the sections (Figure 1). Microscopically, the yellow areas consisted of dense adipose tissue, and the red-brown areas consisted of erythroid, granulocytic, lymphoid, and megakaryocytic cells (Figure 2, 3). Hemorrhagic areas were seen in three of the cases with a hemorrhagic infarction in one of them. Other degenerative findings were dystrophic calcification and hyalinization. Concomitant adrenal cortex adenoma was found in two cases (18.2%). The patients presented with abdominal and back pain, abdominal swelling, and lower urinary tract complaints, and some cases were found incidentally during radiological examination (Table 1). One case had a diagnosis of subclinical Cushing's syndrome. The most common diseases accompanying the cases were type 2 diabetes (2 cases, 18.2%), asthma (2 cases, 18.2%), and hypertension (3 cases, 27.3%) (Table 1). Sarcomatoid urothelial carcinoma of the bladder was reported in one case and benign prostatic hypertrophy (BPH) in another case.

**Figure 1.** Macroscopy of myelolipoma.

### Myelolipomatous Metaplasia

Six myelolipomatous metaplasia cases were detected and all of the cases were located in adrenal cortex adenomas. The patients were between 50-76 years of age (mean: 58); three (50%) were male and three were female. Four of the cases (66.7%) were located on the right, and two (33.3%) were on the left side. Microscopically, scattered fat and hematopoietic tissue elements were detected within the adenomas (Figure 4). Three (50%) cases had a history of hypertension, two (33.3%) had diabetes, and two (33.3%) had asthma (Table 2).

## DISCUSSION

Adrenal lesions with lipomatous components are usually detected incidentally upon radiological examinations of patients for unrelated complaints or investigations for other tumors. These unexpected lesions are mostly removed due to a suspicion of malignancy.[10] Two of these lipomatous lesions which are myelolipoma and myelolipomatous metaplasia include hematopoietic elements in addition to adipose tissue. Although both have similar components, myelolipoma forms a well-circumscribed encapsulated/pseudocapsular mass, whereas myelolipomatous metaplasia is seen as diffuse, poorly circumscribed adipose and myeloid tissue foci within another tumor.[10] Although several authors report similar etiopathogenetic, clinical, and microscopic features, and suggest a developmental link between them, for now, they are considered two different entities.[10] According to some current cytogenetic studies, myelolipoma is a clonal tumor based on nonrandom X chromosome inactivation.[1,14] A study by Chang et al.[15] defined balanced f(3;21) (q25; p11) translocation in tumor cells in one case. New genetic studies in this field will illuminate the origin of these tumors and contribute to the management of these patients.

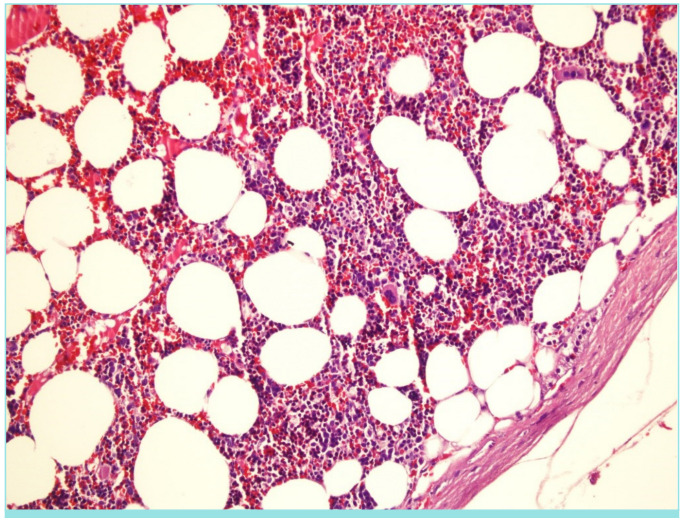

**Figure 2.** Histopathological appearance of myelolipoma composed of mature fat cells mixed with hematopoietic elements. (H&E, x200).

H&E: Hematoxylin & eosin

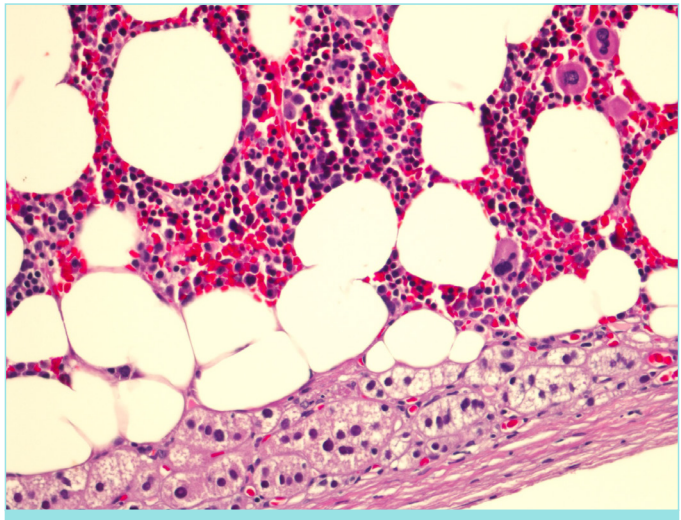

**Figure 3.** Histopathological appearance of myelolipoma composed of mature fat cells mixed with hematopoietic elements. (H&E, x400).

H&E: Hematoxylin & eosin

### Clinical Features

Anbardar et al.[10] reported that adrenal myelolipomas occurred with equal frequency in both sexes while in a large series by Lin et al.[16], 58% of the patients were female. The tumors more frequently involved the right adrenal gland.[10] In our group, female predominance was more prominent (73%) and similarly, right adrenal predilection was higher (82%).

According to the literature, myelomatous change (metaplasia), which is considered a secondary degenerative change, had a female predilection; was mostly on the left adrenal, and the mean age was 52.5 years.[10] Contrarily, our cases were evenly distributed between both genders; mostly located in the right adrenal, and our mean age was higher.

The most common complaints of patients with myelolipoma were reported as abdominal, hypochondrial, and flank pain.[6] Spontaneous retroperitoneal hemorrhage was the most important complication, especially in large myelolipomas and could progress with local back, epigastrium, or flank pain, nausea, vomiting, hypotension, and anemia.[17] Our cases, apart from than the incidental ones, were also admitted to the hospital with abdominal pain and/or distention. In our series, all right-sided lesions were asymptomatic. This might be because, in these anatomical locations, the tumors are more distant from the neural plexuses and peritoneal structures which are sensitive to pressure and irritation.

Investigations on myelolipoma have shown that large and bilateral tumors develop due to external erythropoietin stimulation in hematological disorders such as hereditary spherocytosis, thalassemia intermedia, thalassemia major, or sickle cell anemia.[7,13] Although in our series, we had five large cases of myelolipoma ≥10 cm, these patients did not have a history of hematological disease. Hemorrhage is more common in large tumors, and probably, intratumoral hemorrhages cause tumors to enlarge. However, adrenal myelolipoma cases reported in the literature were generally small (<5 cm) and so far, only two giant cases, 31 cm/6,000 g and 34 cm/5,900 g have been reported.[1,18,19] The myelolipomas in our series were slightly larger than those reported in the literature, possibly related to the high prevalence of hemorrhagic areas.

According to the literature, up to 10% of adrenal myelolipoma cases had hormone hypersecretion.[2,5-7,17] Cases with Cushing's syndrome, primary hyperaldosteronism, pheochromocytoma, or congenital adrenal hyperplasia have been reported.[1,6,11,17] We had one case (0.6 cm)

with a diagnosis of subclinical Cushing's syndrome. Although hormonal hyperactivity was not detected in the majority of our cases, this relationship should be kept in mind in those patients with hormonal pathologies.

In our series, the frequency of hypertension, diabetes, and asthma was high in both myelolipoma and myelolipomatous metaplasia cases similar to the literature.[10] In addition, one of our patients with a myelolipoma was operated on for sarcomatoid urothelial carcinoma of the bladder. In our study, there were BPH patients in both groups. These histories support the hypothesis that chronic diseases, previous operations, and stress states might be associated with these entities.

According to the literature, 5-6% of myelolipoma cases were seen together with adrenocortical adenomas.[6,10,17] This coexistence rate was much higher (18%) in our series. We plan to observe and re-analyze this rate in larger groups.

Myelomatous change was usually observed in adrenocortical adenomas and more rarely, in adrenocortical carcinomas, pheochromocytomas, and ganglioneuromas.[6,20] Adrenal pathology was reported as adrenocortical adenoma in 70% of the cases examined by Anbardar et al.[10] In our group, all myelomatous metaplasia cases were associated with adrenocortical adenomas. The rest of the cases in Anbardar et al.'s[10]

**Table 1. Clinicopathological features of myelolipoma cases**

| Case no | Age, gender | Location | Size | Patient complaints and history | Surgical procedure | Radiological and other findings |
|---|---|---|---|---|---|---|
| 1 | 64, F | Right adrenal | 11 cm | No complaints. | Right adrenalectomy | Diffuse hemorrhagic areas on microscopy. |
| 2 | 47, F | Right adrenal | 2.7 cm | Abdominal and back pain. | Right adrenalectomy | Association with adrenal cortex adenoma. |
| 3 | 31, F | Right adrenal | 10 cm | No complaints.<br>The mass was detected in the right adrenal gland during follow-ups 2.5 years previously; no surgical intervention was made.<br>A diagnosis of asthma. | Right adrenalectomy | Radiological preliminary diagnosis: Exophytic angiomyolipoma in the upper pole of the right kidney?<br>Hamartoma tumor of right adrenal origin?<br>Secondary degeneration (hemorrhagia and hyalinization). |
| 4 | 55, F | Right adrenal | 0.6 cm | A diagnosis of asthma, DM and HT.<br>Upon routine endocrine follow-up, bilateral adrenal adenoma was detected.<br>Diagnosis of subclinical Cushing's syndrome. | Laparoscopic right adrenalectomy | Abdominal US: appearance thought to be compatible with adenoma.<br>Association with adrenal cortex adenoma. |
| 5 | 52, F | Right adrenal | 4.5 cm | No complaints. | Right adrenalectomy | Radiological diagnosis: Adenolipoma?<br>Hemorrhagic areas. |
| 6 | 72, F | Left adrenal | 10 cm | Abdominal pain and swelling.<br>History of HT, DM, CAD. | Left adrenalectomy | Whole abdomen and diffusion MRI: Adenoma?<br>Diffuse hemorrhagic infarction, dystrophic calcification, significant hyalinization, and lymphocyte infiltration in capsule. |
| 7 | 50, M | Right adrenal | 8 cm | Lower urinary tract symptoms.<br>History of HT. | Right laparoscopic adrenalectomy | Radiological diagnosis:<br>Left adrenal lipoma? Angiomyolipoma? |
| 8 | 56, M | Right adrenal | 10 cm | Abdominal pain. | Right adrenalectomy | Radiological diagnosis: Adrenal adenoma? |
| 9 | 46, F | Right adrenal | 11.5 cm | No complaints. | Right adrenalectomy | Radiological diagnosis: Myelolipoma? |
| 10 | 67, F | Right adrenal | 4 cm | No complaints.<br>History of surgery for sarcomatoid urothelial bladder carcinoma. | Right adrenalectomy | MRI: Heterogeneous mass lesion measuring approximately 3.6x4.4 cm with subcentimetric calcifications in the right adrenal gland, without F18-FDG uptake. |
| 11 | 70, M | Left adrenal | 4.5 cm | No complaints.<br>History of BPH. | Left adrenalectomy | US preliminary diagnosis: Adenoma?<br>Adrenal gland CT.<br>Radiologic diagnosis: Neoplasm of the adrenal gland with unclear or unknown behavior. |

BPH: Benign prostatic hypertrophy, CAD: Coronary artery disease, CT: Computerized tomography, DM: Diabetes mellitus, F: Female, FDG: Fluorodeoxyglucose, HT: Hypertension, M: Male, MRI: Magnetic resonance imaging, US: Ultrasound.

study were oncocytoma, cavernous hemangioma, adrenal hyperplasia, or adrenocortical neoplasms with unknown malignant potential. In our study, there was one patient who had undergone cholecystectomy and one patient with BPH in the myelolipomatous metaplasia group.

### Radiological Features

Ninety percent of adrenal myelolipoma cases are detected by computed tomography (CT) and magnetic resonance imaging. A radiological diagnosis of at least 50% of them depends on observing an adrenal mass consisting of fat.[1,10] Lipomatous retroperitoneal lesions like lipoma, teratoma, angiomyolipoma, well-differentiated liposarcoma, adrenocortical adenoma/carcinoma, and extramedullary hematopoiesis are included in the radiological differential diagnosis.[8,11] Among our cases, the preliminary diagnoses in those who underwent radiological examination were angiomyolipoma developing exophytically from the upper pole of the right kidney; hamartomatous tumor of right adrenal origin; adrenal adenoma; and adrenal lipoma. The exclusion of pheochromocytoma, the suspicion of malignancy, and the fact that biopsy findings change the treatment are generally accepted indications for adrenal biopsy.[1] CT-guided fine-needle aspiration biopsy (FNAB) is recommended for diagnosis by some authors.[11] FNAB was not performed on any of our myeloma cases, and the precise diagnosis was achieved after the histological examination of the resection materials.

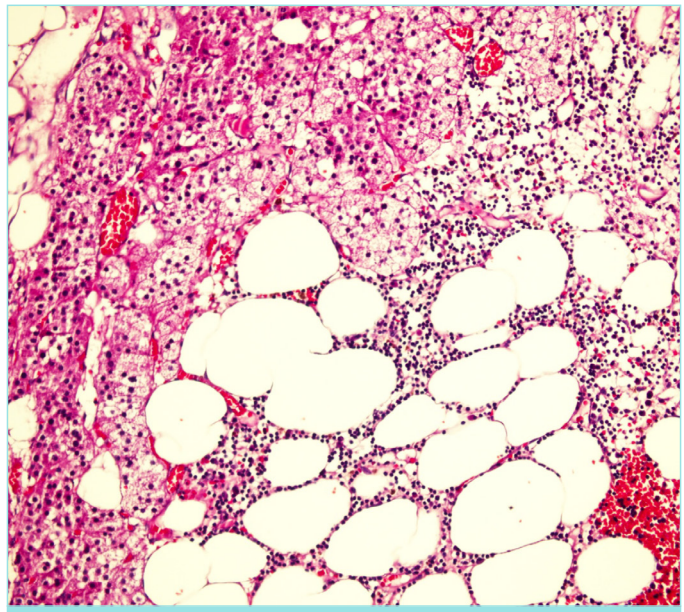

**Figure 4.** Histopathological appearance of myelolipomatous metaplasia (H&E, x100).

H&E: Hematoxylin & eosin

**Table 2. Clinicopathological features of the cases with myelolipomatous metaplasia**

| Case no | Age, gender | Location | Size | Patient complaints and history | Surgical procedure | Adrenal neoplasia and radiological findings |
|---|---|---|---|---|---|---|
| 1 | 56, M | Left adrenal | 9 cm | No complaints. | Left adrenalectomy | Adrenal cortex adenoma |
| 2 | 51, M | Right adrenal | 6 cm | No complaints.<br>Mass detected in the right adrenal gland upon routine check-up. | Right adrenalectomy | Adrenal cortex adenoma |
| 3 | 50, F | Left adrenal | 10 cm | No complaints.<br>History of HT and DM. | Left adrenalectomy | Adrenal cortex adenoma<br>MRI: mass lesion in the left adrenal gland measuring 40x33 mm, showing intense suppression; may be compatible with adenoma. |
| 4 | 76, F | Right adrenal | 5.7 cm | Palpitations and sweating.<br>History of DM. | Right adrenalectomy | Adrenal cortex adenoma<br>Whole abdomen and diffusion MRI: heterogeneous-appearing mass lesion with cystic areas measuring 29x53x46 mm and contrasting heterogeneously observed in the right adrenal gland. |
| 5 | 67, M | Right adrenal | 5.5 cm | No complaints.<br>History of BPH, HT, asthma, cholecystectomy, and lumbar hernia intervention (surgical). | Right adrenalectomy | Adrenal cortex adenoma |
| 6 | 48, F | Right adrenal | 7.5 cm | Headache.<br>History of asthma and HT. | Right adrenalectomy | Right adrenal cortex adenoma measuring 5 cm.<br>Radiological diagnosis: Pheochromocytoma? |

BPH: Benign prostatic hypertrophy, DM: Diabetes mellitus, F: Female, HT: Hypertension, M: Male, MRI: Magnetic resonance imaging.

### Management

Current guidelines on the management of adrenal incidentalomas do not require hormonal investigations when the definite diagnosis is myelolipoma.[8,17] However, an endocrinological examination is useful in younger patients with hypertension, diabetes, or prediabetes, and for bilateral cases.[1] Surgery is recommended in myelolipomas presenting with complaints such as pain and swelling or symptoms related to hormone secretion, and in cases larger than 5 cm due to the risk of spontaneous rupture and retroperitoneal hemorrhage.[1,7,9,11] Myelolipomas smaller than 5 cm are usually asymptomatic, have no indication for surgical intervention, and are followed up with imaging studies.[21]

## CONCLUSION

Adrenal myelolipoma are rare entities which are usually detected incidentally. They have a similar histopathological appearance and probably a similar origin to myelolipomatous metaplasia. In lipomatous adrenal lesions which develop based on chronic diseases, myelolipoma and an adrenal entity with myelolipomatous metaplasia should be kept in mind.

### MAIN POINTS

- Adrenal myelolipoma is a rare entity which is usually detected incidentally.
- It is composed of adipose and hematopoietic tissue, and has a similar histopathological appearance and probably a similar origin to myelolipomatous metaplasia.
- Adrenal myelolipoma is encapsulated, while myelolipomatous metaplasia is a diffuse lesion mostly located in an adrenal adenoma.
- They both frequently coexist with chronic diseases such as hypertension, diabetes, and asthma.

## ETHICS

**Ethics Committee Approval:** University of Health Sciences Türkiye, Kartal Dr. Lütfi Kıdar City Hospital Clinical Research Ethical Committee (approval number: 2022/514/220/13, date: 22.02.2022).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: M.A., C.C.B., Concept: S.Ş., A.E.G., S.H.K., Y.S.G., M.A., C.C.B., N.Ö.B., N.E., Design: S.Ş., A.E.G., S.H.K., Y.S.G., M.A., C.C.B., N.Ö.B., N.E., Data Collection and/or Processing: A.E.G., S.H.K., N.Ö.B., Analysis and/or Interpretation: S.Ş., A.E.G., S.H.K., Y.S.G., M.A., C.C.B., N.Ö.B., N.E., Literature Search: S.Ş., Y.S.G., Writing: S.Ş., A.E.G., S.H.K., Y.S.G., M.A., C.C.B., N.Ö.B., N.E.

## DISCLOSURES

**Conflict of Interest:** No conflict of interest was declared by the authors.

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