Evaluation of 61 Secondary Amyloidosis Patients: A Single-Center Experience from Turkey

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Evaluation of 61 Secondary Amyloidosis Patients: Türkiyeden Tek Merkez Deneyimi

ÖZET
Amaç: Sekonder amiloidoz hastaların demografik, klinik ve laboratuar özelliklerini, hastalığın sebeplerini, MEFV gen mutasyonlarını ve mortalite oranlarını değerlendirilmiştir. Gereç ve Yöntem: 2007-2013 arasında Cumhuriyet Üniversitesi, Tıp Fakültesi, Nefroloji kliniği başvuran böbrek veya rektal doku biyopsisiyle sekonder amiloidoz tanısı alan toplam 61 hasta çalışmaya dahil edildi. Demografik özellikler, sekonder amiloidoz sebepleri, MEFV gen mutasyonları, ve son dönemde böbrek yetmezliği (SDBY), renal transplantasyon ve mortalite oranları retrospektif olarak değerlendirildi. Bulgular: Etiyolojik açıdan hastaların %62.2’si (38) FMF, %9.8’i (6) bronşiyektazi ve amfizem, %4.9’u (3) tüberkuloz, %3.2’si (2) FMF ve anıkozan spondilit birliği, %1.6’sı (1) FMF ve romatoid artrit birliği, %1.6’sı (1) FMF ve sistemik lupus eritematosus birliği, %1.6’sı (1) osteomyelit, %1.6’sı (1) septikt artrit, %1.6’sı (1) kron hastalığı, %1.6’sı (1) kolon kanseri, %1.6’sı (1) bronşiyektazi ve tüberkuloz birliği, %1.6’sı (1) romatoid artrit ve %6.5’i (4) idiopatik olarak değerlendirildi. Sekonder amiloidozu olan 47 hastanın 32’sinde (%68) nefrotik düzeyde proteinürü saptandı. Sekonder amiloidozlu 45 hastanın MEFV gen mutasyonları incelendi. Hastaların çoğunda M694V mutasyonu vardı. Surprizli bir şekilde, 3 vakada heterozigot E148Q mutasyonu saptadık. 12 vaka öldü ve bu hastaların 9’u SDBY’idi. SDBY olan 5 vaka böbrek nakliydi. Tahmin: Bu çalışmada sekonder AA amiloidoz için en yaygın sebep olarak MEFV mutasyonu bulundu. Daha büyük studies ile daha geniş kohortlarda daha iyi sonuçlar elde edilebilir.

Anahtar Kelimeler
AA Amiloidoz; Ailevi Akdeniz Ateşi; MEFV

ABSTRACT
Aim: To evaluate demographic, clinical and laboratory characteristics, causes, MEFV gene mutations, and mortality rates of patients with secondary amyloidosis. Material and Method: 61 patients who had been diagnosed with secondary amyloidosis by renal and rectal biopsy between 2007 and 2013 in the nephrology clinic of Cumhuriyet University, Faculty of Medicine, were included in the study. Demographic characteristics, causes of secondary amyloidosis, MEFV gene mutations, end-stage renal failure (ESRF), renal transplantation, and mortality rates were examined retrospectively. Results: In etiological terms, Familial Mediterranean Fever (FMF) occurrence was 62.2% (38), bronchiectasis and emphysema 9.8% (6), tuberculosis 4.9% (3), coexistence of FMF and ankylosing spondylitis 3.2% (2), coexistence of FMF and rheumatoid arthritis 1.6% (1), coexistence of FMF and systemic lupus erythematosus (SLE) 1.6% (1), osteomyelitis 1.6% (1), septic arthritis 1.6% (1), Crohn’s disease 1.6% (1), colon cancer 1.6% (1), coexistence of bronchiectasis and tuberculosis 1.6% (1), rheumatoid arthritis 1.6% (1), and idiopathic cases 6.5% (4). Proteinuria was determined at nephrotic level among 68% (32) of patients who had secondary amyloidosis. MEFV gene mutation of 45 patients with secondary amyloidosis was assessed. Most patients had M694V gene mutation. Surprisingly, we detected heterozygous E148Q mutation in 12 cases. 9 of these had ESRF. Five cases with ESRF underwent renal transplantation. Discussion: We found FMF as the most common cause for secondary AA amyloidosis in this study. Further studies should be done with larger or multicenter cohorts.

Keywords
AA Amyloidosis; Familial Mediterranean Fever; MEFV

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Evaluation of 61 Secondary Amyloidosis Patients

Introduction
Amyloidosis is a large group of diseases caused by extracellular and/or intracellular accumulation of amyloid fibril proteins due to different etiologies [1]. Accumulations are regarded as localized if seen in one organ or as systemic if seen in multiple organs. Accumulations are mostly seen in the brain, heart, kidney, liver, and digestive systems. Amyloid accumulations in organs other than the brain are generally observed as systemic. In time, the increase of amyloid accumulation causes pressure on the cells. Then atrophic changes in cells and tissue destruction occur. Also, organ dysfunctions occur due to the direct toxic effects of accumulated fibril proteins. Different clinical findings may be observed depending on the amyloid accumulation areas (localized and systemic forms) [1, 2].

Systemic amyloidosis types are mainly classified as primary (immunoglobulin light chain or AL) amyloidosis, secondary (AA) amyloidosis, and familial (hereditary) amyloidosis. To date, approximately 31 different proteins have been identified as causing amyloidosis. These proteins are structurally different from each other [3, 4].

The cause of secondary amyloidosis is an acute phase reactant known as serum amyloid A (SAA) which is the precursor protein of AA amyloidosis. The most common causes of secondary AA amyloidosis are rheumatic diseases, chronic infections, chronic arthritis, auto-inflammatory diseases, and malignancies and rheumatoid arthritis (RA) in particular [5]. The common feature of secondary amyloidosis is chronic inflammation, which is seen in all cases. SAA is synthesized in the liver through the effect of cytokines such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor (TNF)-alpha and circulates in the bloodstream as a part of high-density lipoprotein 3 fractions (HDL3) [6]. Although the main source of SAA protein is the liver, it is also synthesized in endothelial cells, macrophages, atherosclerotic smooth muscle cells, the brain, and synovium. A high SAA level alone does not cause amyloid accumulation, however it leads to macrophage activation and increased secretion of cytokines such as IL-1, IL-6, and TNF-alpha. This, in turn, is followed by amyloid accumulation. Amyloid accumulation is primarily seen in the spleen, liver and kidneys, and AA amyloidosis can lead to nephrotic syndrome and ESRD [6, 7]. Clinical findings of amyloidosis vary based on the organ involved. Proteinuria develops in renal involvement as a result of accumulation of amyloid fibrils. Proteinuria is more commonly involved. Proteinuria develops in renal involvement as a result of accumulated fibril proteins. Different clinical findings may be observed depending on the amyloid accumulation areas (localized and systemic forms) [1, 2].

Statistical Analysis
All statistical analyses were performed by SPSS version 22.0 (SPSS IBM, Armonk, NY, USA). All demographic data and clinical findings were expressed as mean ± standard deviation (and range) with a 95% confidence interval.

Results
A total of 61 patients diagnosed with secondary amyloidosis were included in the current study. Their mean age was 49.81±17.93. 41 (67.2%) of these patients were male and 20 (32.7%) were female. While the mean age of men was 47.60±16.60 the mean age of women was 54.35±20.07. Table
MEFV mutation analysis was performed in 45 cases with secondary amyloidosis. Table 3 illustrates MEFV gene mutations of patients. Homozygous or heterozygous M694V gene mutations were determined in most of the cases. There was also coexistence of several gene mutations. R202Q mutation, rarely analyzed, was identified in 4 cases and only one case had RA in addition to FMF. We identified 3 patients with E148Q mutation. Fourteen patients had one heterozygous mutation. In mutation analysis of 9 phenotype II patients, it was found as homozygous M694V and homozygous R202Q (1), heterozygous M694V (3), homozygous M680I (G/C) (2), heterozygous V726A and heterozygous F479L (1), heterozygous R202Q 4 (6.5%), homozygous M680I (G/C) (2 (3.2%), homozygous M680I (G/C) and Heterozygous V726A (1 (1.6%), Heterozygous E148Q (3 (4.9%), Heterozygous M694V and Heterozygous R202Q (1 (1.6%), Heterozygous M694V and Heterozygous R202Q (1 (1.6%), Heterozygous M694V and Heterozygous R761H (1 (1.6%), Heterozygous M694V and Heterozygous V726A (1 (1.6%), Heterozygous M694V, Heterozygous R202Q and Heterozygous V726A (1 (1.6%)


Table 1. Demographic and laboratory findings of patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>Mean±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61</td>
<td>49.81 ± 17.93</td>
<td>(17-84)</td>
</tr>
<tr>
<td>Male</td>
<td>41</td>
<td>47.6 ± 16.6</td>
<td>(17-78)</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>54.35 ± 20.07</td>
<td>(23-84)</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>61</td>
<td>39.77 ± 34.26</td>
<td>(8-210)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>61</td>
<td>3.82 ± 3.92</td>
<td>(0.3-24)</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>61</td>
<td>5.57 ± 1.24</td>
<td>(2.6-7.8)</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>61</td>
<td>2.31 ± 1.00</td>
<td>(0.2-4.2)</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>61</td>
<td>19.36 ± 27.99</td>
<td>(5-225)</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>61</td>
<td>22.75 ± 26.91</td>
<td>(4-219)</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>61</td>
<td>11.41 ± 2.46</td>
<td>(5.4-16.7)</td>
</tr>
<tr>
<td>HCT (%)</td>
<td>61</td>
<td>34.48 ± 6.85</td>
<td>(16-48.5)</td>
</tr>
<tr>
<td>Sedimentation (mm/hour)</td>
<td>54</td>
<td>76.31 ± 35.72</td>
<td>(7-145)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>56</td>
<td>44.42 ± 47.23</td>
<td>(3-220)</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>58</td>
<td>120.74 ± 20.85</td>
<td>(36-425)</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>53</td>
<td>33.3 ± 13.1</td>
<td>(13-83)</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>56</td>
<td>185.19 ± 85.4</td>
<td>(91-95)</td>
</tr>
<tr>
<td>Microalbuminuria (g/day)</td>
<td>47</td>
<td>3.24 ± 3.25</td>
<td>(0.1-13)</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>47</td>
<td>6.49 ± 5.02</td>
<td>(0.5-22.8)</td>
</tr>
</tbody>
</table>


Table 2. Primary diseases causing amyloidosis

<table>
<thead>
<tr>
<th>Primary disease</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>4 (6.5%)</td>
</tr>
<tr>
<td>FMF</td>
<td>38 (62.2%)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>3 (4.9%)</td>
</tr>
<tr>
<td>Bronchiectasis and emphysema</td>
<td>6 (9.8%)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>RA</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>FMF and AS</td>
<td>2 (3.2%)</td>
</tr>
<tr>
<td>FMF and SLE</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>FMF and RA</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Bronchiectasis and tuberculosis</td>
<td>1 (1.6%)</td>
</tr>
</tbody>
</table>

these patients were considered as high. Sedimentation was examined for 54 patients. The results of 49 of these patients were found to be high because of the level exceeded 25 mm/h. All patients except for 2 had low serum albumin levels (serum albumin < 4 gr/dl).

Lipid levels of patients with secondary amyloidosis were found to be generally normal; however, the HDL levels were found to be low in 73.6% (39) of patients. Twenty-eight of 38 cases with FMF had low HDL levels, 3 patients had high HDL levels, and 7 had normal HDL levels. Eight of the excess cases had low HDL levels, 2 had normal HDL levels and one had high HDL level. Two of 10 cases whose LDL levels were above 160 mg/dl had proteinuria at nephrotic level. Ten of 16 patients whose triglyceride level was above 200 mg/dl had proteinuria above 1-3.5 gr and 8 had proteinuria above 3.5 gr. All of the 8 patients whose triglyceride level was above 200 mg/dl had proteinuria at nephrotic level. Ten of 16 patients whose cholesterol level was above 200 mg/dl had proteinuria at nephrotic level and 5 had 1-3.5 gr proteinuria. The cholesterol level of one patient was not measured.

In the current study, of 61 amyloidosis patients, 56 patients had complete urine analyses, 39 of these patients had proteinuria, 16 had hematuria in addition to proteinuria, and one patient had only hematuria. Proteinuria was determined at nephrotic level among 68% (32) of 47 patients who had secondary amyloidosis. All patients except for 2 had hypoalbuminemia (serum albumin < 4 gr/dl). While hepatomegaly was found in 5 (8.3%) cases, splenomegaly was found in 9 (15%) cases.

In the current study, of 61 amyloidosis patients, 5 patients had renal transplants and also all of the cases who had renal transplants were diagnosed with FMF phenotype I. MEFV mutation results of cases who underwent transplantations were identified as: homozygous M694V (1), heterozygous M694V and heterozygous E148Q (2), heterozygous V726A and heterozygous F479L (1). Mutation analysis of one patient was not performed. Three patients had proteinuria at nephrotic level, one patient had proteinuria between 1-3 gr/day, and proteinuria of one patient was not examined. None of these patients had repeated proteinuria in renal allograft.

Discussion
Secondary amyloidosis is defined as the accumulation of amyloid on tissues and organs as a result of increasing SAA protein, which is an acute phase reactant developing in conjunction with inflammation. SAA production increases in inflammatory conditions [6]. In the current study, we evaluated demographic characteristics, etiology and mortality rates, and MEFV gene mutations of 61 secondary amyloidosis patients who were admitted to our clinic.

Although in Europe the most common cause of amyloidosis is RA, in Turkey the most common cause of amyloidosis is FMF [18]. Amyloid may develop in a period between 2 months and 14 years after FMF episodes. The period leading to ESRF after proteinuria may be 2-13 years [19]. Secondary AA amyloidosis remains the most serious manifestation of FMF. The incidence rate of secondary AA amyloidosis among FMF patients is 37% in sephardic Jews, 24% in Armenians, 8% in Ashkenazi Jews, 12% in Turks and 10% in Arabs [20, 21]. Amyloidosis development rates among FMF patients were found as 25.7% in homozygous M694V mutation, 15.4% in M694V compound heterozygous and 12.3% in other mutations. Amyloidosis did not develop in E148Q mutations [22]. Although heterozygous E148Q mutation was found in non-amyloid glomerular diseases [23, 24], there is still no data about whether heterozygous E148Q mutation is an amyloidosis-causing mutation. Topaloglu et al. analyzed 26 patients homozygous for E148Q, 10 compound heterozygous for E148Q, and 8 complex cases. They found that none of their patients had amyloidosis except that 2 cases with E148Q/E148Q mutation had a family history of amyloidosis and one had rapidly progressive glomerulonephritis [25]. Balci et al. investigated AA amyloidosis patients (25 phenotype II) in terms of 4 MEFV mutations (M694V, M680I (G/C), V726A and E148Q), and they observed M694V mutation as the most frequent mutation in homoyzgous, heterozygous and compound heterozygous states. In their study, E148Q was found as compound heterozygous with M694V mutation in 2 cases [26]. In a study conducted with 507 children with FMF in the southeast of Turkey, renal amyloidosis developed in 1.4% (n=7) of patients. Five of the patients with renal amyloidosis had homozygous M694V mutation and two of them were compound heterozygous with M694V/V726A and M694V/M680I (G/C) mutations. Two of these patients with amyloidosis were phenotype II FMF patients [27]. In a study evaluating frequency of MEFV mutations in FMF patients, it was found that 16 patients had a history of amyloidosis (3.55%). Among the cases with amyloidosis, 12 cases had M694V homozygous, one case had compound heterozygous for M694V and M680I (G/C) mutations, and one case had a complex allele for E148Q/E148Q/M694V mutations. No mutation could be detected in 2 cases with amyloidosis [28]. In Jewish renal amyloidosis patients, M694V/M694V genotype was found as the most frequent mutation. However, E148Q mutation was found as compound heterozygous state together with exon 10 mutation of MEFV gene [16, 17].

In this study, in terms of MEFV gene mutation, M694V mutation was 19.6% (homozygous 7 and heterozygous 5), M694V compound heterozygous frequency was 11.4%, M680I (G/C) mutation was 6.5% (homozygous 2 and heterozygous 2), heterozygous E148Q was 4.9% (3), and heterozygous R202Q was 6.5% (4). The number of patients with at least one exon 10 of MEFV gene mutation was 30. At least one M694V mutation was detected in 25 patients (Table 3). Our MEFV gene mutation results, especially for M694V, were in accordance with the literature. However, we identified 3 patients with E148Q mutation, which is not reported in European publications to cause amyloid accumulations. We think that this is an interesting finding, and this information can bring a new perspective to the literature about E148Q mutation and development of amyloidosis. Because amyloid accumulation leads to renal failure, it is the most important complication in FMF patients. However, it is not related to the severity of the disease. It can also appear among FMF patients who have rare and mild attacks. Additionally, phenotype II FMF can be observed among patients with no clinical symptom experience [29]. Long-term plasma SAA level should be high for AA amyloidosis development [2]. In a study, SAA levels were determined to be high in 40% of clinical phenotype III cases [30]. Clinical findings of mild FMF were observed in heterozygous persons. Acute phase responses were
higher among heterozygous persons than in the healthy control group [30, 31]. Similarly, amyloid accumulation was determined in non-compound heterozygous cases in our study. In addition, 9 cases with FMF phenotype II were determined. During diagnosis, ESRF was observed in 5 of these patients.

The frequency of amyloidosis in autopsies in Western countries has varied between 0.50% and 0.86%. According to the reported series in England and USA, more than half of the cases have juvenile and adult RA. Ankylosing spondylitis is the second most frequent cause with rates up to 12%. It is followed by psoriatic arthritis with the rate of 4-5% [32-34]. AA amyloidosis is a rare complication of RA. However, there have been significant differences among publications. AA amyloid prevalence in RA ranges between 4% and 26% in literature [35]. AA amyloid was higher (14-61%) in RA patients in the post-mortem period [36]. Similarly, one patient had RA and one patient had coexistence of FMF and RA in our study. The most common cause of secondary amyloidosis in Turkey is reported as FMF [18]. Furthermore, the RA-related secondary amyloidosis frequency has been found to be low. In 2 studies conducted in ankylosing spondylitis patients who lived in Europe, amyloidosis rates were 7% and 9% respectively, as determined by rectal and fat biopsy screenings [37, 38]. In the current study, we found 2 (3.2%) cases who had coexistence of ankylosing spondylitis and FMF.

In the current study, there was 3 occurrences of tuberculosis, one of osteomyelitis, one of septic arthritis, and one coexistence of bronchiectasis and tuberculosis among patients with infectious diseases. As in other studies, the most common cause of infectious diseases was found to be tuberculosis in our study. Tuberculosis is the most commonly seen of the chronic infections that cause secondary AA amyloidosis; it is followed by osteomyelitis, chronic bronchitis, chronic muco-cutaneous ulcer, leprosy, Q fever, and subacute bacterial endocarditis [1].

In a study that included 287 secondary amyloidosis patients from 11 centers in Turkey, the etiological causes were determined as FMF in 64% of patients, tuberculosis in 10%, bronchiectasis and chronic obstructive pulmonary disease in 6%, RA in 4%, spondyloarthropathies in 3%, chronic osteomyelitis in 2%, other causes in 4%, and idiopathic in 7%. While hepatomegaly was 17%, splenomegaly was 11% [18]. In another study that evaluated 59 renal amyloidosis cases, 18 patients (30.5%) were found to have FMF, 12 (20.3%) had pulmonary tuberculosis, 8 (13.5%) had chronic osteomyelitis, 9 (15.2%) had bronchiectasis, 4 (11.8%) had RA, one (1.6%) had Castleman disease, and 7 (11.8%) were idiopathic [39]. In a study including 40 amyloidosis patients between 2003 and 2009 in Egypt, secondary amyloidosis was determined in 32 of patients and primary amyloidosis was determined in 8 patients. 30% of secondary amyloidosis cases (12) were FMF, 20% (8) were pulmonary tuberculosis, 10% (4) were chronic osteomyelitis, 10% (4) were bronchiectasis, 7% (3) were RA, and 2% (1) were rheumatic heart disease [40]. In another study, the most common cause of secondary amyloidosis was RA, which was followed by recurrent pulmonary infections at the rate of 11%, Crohn’s disease at 5%, ankylosing spondylitis at 5%, tuberculosis at 3%, osteomyelitis at 2%, FMF at 2%, Hodgkin’s lymphoma at 2%, and idiopathic cases at 5% [41].

In a multicenter study conducted in Australia and New Zealand, 58,422 patients who underwent renal replacement treatments between 1963 and 2010 were examined. 490 (0.8%) of these patients had problems related to secondary amyloidosis. Survival rates of patients with dialysis-induced secondary amyloidosis were found to be worse and renal allograft survival and renal allograft recurrence were worse compared to those related to other diseases. A significant number of deaths were observed due to amyloidosis complications in amyloidosis-related ESRF. When amyloidosis-related ESRF and ESRF related to other causes were compared, cardiac death rates were 37% and 41%, respectively. However, death from heart failure was more common in the amyloidosis-related group (8.6% vs. 2.2%). No difference was found between the 2 groups in the 10-year follow-up in terms of dialysis interruption, infection, cancer, and other causes of death [42]. One, 2 and 6-year survival rates in the retrospective analysis of 48 ESRF patients with systemic amyloidosis (72%, 62%, and 44% respectively) were significantly lower compared to non-diabetic controls (95%, 91%, and 81%) [43]. In our study, 35 patients were diagnosed with ESRF and transferred to hemodialysis. In a retrospective study performed with 23 amyloidosis patients who underwent renal transplant operations, 10-year patient and graft survival rates were found as 66% and 68% respectively, and no significant difference was found between them and 47 non-amyloidosis control patients (57% and 87%). Recurrent amyloid rates in renal allograft were 4.3% [44]. In a study comparing 45 amyloidosis transplant receivers and 45 control patients, 3-year patient survival rates were 51%, compared to 79% in the control group. Graft survival was 45% as opposed to 58% in the control group. Recurrent amyloidosis rate in renal allograft was 9% [45]. In this study, 5 patients underwent renal transplant. No amyloid developed in renal allograft cases.

It is important to form a clinical picture of FMF in Turkey, especially in the province of Sivas where FMF is most frequently observed [12-14]. Screening of individuals who have FMF in their family histories and evaluating the treatments of phenotype III cases that have mutations but do not show clinical symptoms are prominent issues to be examined. Although studies have been conducted on phenotype II cases, when we consider that secondary amyloidosis can also develop in non-compound heterozygous mutations, it should be clarified through future studies whether phenotype III cases should be detected in early stages and treated through the evaluation of acute phase reactants.

As stated in other studies conducted in Turkey, we found FMF to be the most common cause of secondary amyloidosis. Surprisingly, we detected heterozygous E148Q mutation in 3 cases with amyloidosis. This finding can bring a new perspective to the literature about E148Q mutation and the development of amyloidosis. We suggest that further studies should be done with larger or multicenter cohorts.

**Compliance with Ethical Standards**

Ethical approval: The Ethics Committee of Cumhuriyet University, Faculty of Medicine approved the present study. The study was conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
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Competing interests

The authors declare that they have no competing interests.

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