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# Adrenal Insufficiency as the First Manifestation of AA Amyloidosis in a Patient with Familial Mediterranean Fever: A Case Report

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**Abstract**

**Background:** Familial Mediterranean Fever (FMF) is the most common monogenic autoinflammatory disease, and AA amyloidosis is its most severe complication. While AA amyloidosis predominantly affects the kidneys, adrenal involvement is exceptionally rare and infrequently reported.

**Case Presentation:** A 32-year-old man on chronic hemodialysis for end-stage renal failure due to amyloid nephropathy was referred for chronic abdominal pain, hypercalcemia (> 115 mg/L), hyponatremia (130 mmol/L), and severe intradialytic hypotension. He reported that his typical FMF attacks had ceased after starting hemodialysis; however, he had recently developed new, continuous symptoms, including intense asthenia and chronic abdominal pain. Physical examination revealed progressive hyperpigmentation on sun-exposed areas. Endocrinological work-up confirmed primary adrenal insufficiency (very high ACTH with low cortisol). An abdominal CT scan showed bilateral adrenal calcifications. The patient's history included recurrent febrile episodes since childhood and a family history suggestive of FMF. AA amyloidosis was confirmed via salivary gland biopsy, and genetic testing revealed a homozygous M694I mutation in the *MEFV* gene. The patient was started on hydrocortisone replacement therapy. Despite initial improvement, he died one year later from complications related to advanced AA amyloidosis, including severe diarrhea and malnutrition.

**Conclusions:** This case illustrates the rare occurrence of adrenal insufficiency due to AA amyloidosis in FMF. It highlights the need to screen for adrenal insufficiency in dialysis patients presenting with chronic abdominal pain, unexplained hypercalcemia, or intradialytic hypotension. The presence of adrenal calcifications on abdominal CT should raise suspicion for this diagnosis. Most importantly, this case underscores that FMF is prevalent in Algeria and that AA amyloidosis and its devastating complications can be prevented by early initiation of colchicine therapy in childhood. Increased awareness and early diagnosis are crucial to avert such tragic outcomes.

**Keywords:** Familial Mediterranean Fever, AA Amyloidosis, Adrenal Insufficiency, Hypercalcemia, Hemodialysis, Adrenal Calcifications, Hyperpigmentation, Colchicine, Algeria

## 1. Introduction

Familial Mediterranean Fever (FMF) is the most prevalent monogenic autoinflammatory disease worldwide, primarily affecting populations of Mediterranean descent, including Armenians, Turks, Arabs, and Jews [1]. In Algeria, FMF is common, with the *MEFV* M694I mutation being the most frequent [2]. The disease results from mutations in the *MEFV* gene, which encodes pyrin, a protein crucial for regulating inflammasome activity and interleukin-1β production [1, 3].

The most feared long-term complication of FMF is AA amyloidosis, a consequence of chronic inflammation. This condition leads to the deposition of amyloid fibrils in various organs, with the kidneys being the most common site, ultimately resulting in end-stage renal disease (ESRD) [4]. Although adrenal involvement is rarely reported clinically, post-mortem studies have occasionally identified amyloid deposits in the adrenal glands [5, 6].

We report an original case where primary adrenal insufficiency, caused by adrenal AA amyloidosis, was the presenting feature in a patient with FMF who was already on chronic hemodialysis for amyloid nephropathy. This case serves as a powerful

reminder of the severe consequences of a late FMF diagnosis and emphasizes the critical importance of early colchicine therapy.

## 2. Case Presentation

### 2.1 Patient Presentation and History

A 32-year-old man, born to non-consanguineous parents, was referred to our nephrology department from the gastroenterology service due to chronic abdominal pain, hypercalcemia (> 115 mg/L), and hyponatremia (130 mmol/L). He had been on chronic hemodialysis for six months for end-stage renal disease secondary to biopsy-proven amyloid nephropathy of an indeterminate type. His recent clinical course was further complicated by severe episodes of intradialytic hypotension, profound asthenia, and diffuse muscle weakness.

His medical history was significant for unexplained, recurrent febrile episodes since childhood, which were consistent with FMF attacks. Interestingly, these typical attacks had completely ceased after he began hemodialysis. However, over the preceding two months, he had developed a new, continuous set of symptoms, distinct from his previous intermittent flares. This new presentation was characterized by persistent and debilitating fatigue, chronic abdominal pain, and progressive weakness. A family history revealed that a cousin, also on dialysis, presented with a similar clinical picture. Additionally, the patient had a history of a multinodular goiter that required surgical management; subsequent thyroid function tests showed low T3 and T4 levels suggestive of peripheral hypothyroidism.

### 2.2 Clinical and Laboratory Findings

Physical examination revealed a striking, progressive generalized hyperpigmentation, particularly prominent on sun-exposed areas (face, neck, and hands), which had developed over the six months of hemodialysis (Fig 1). An abdominal scar from a previous episode of "white peritonitis" was noted (Fig 2), and a scar from his goiter surgery was visible on the neck (Fig 3).

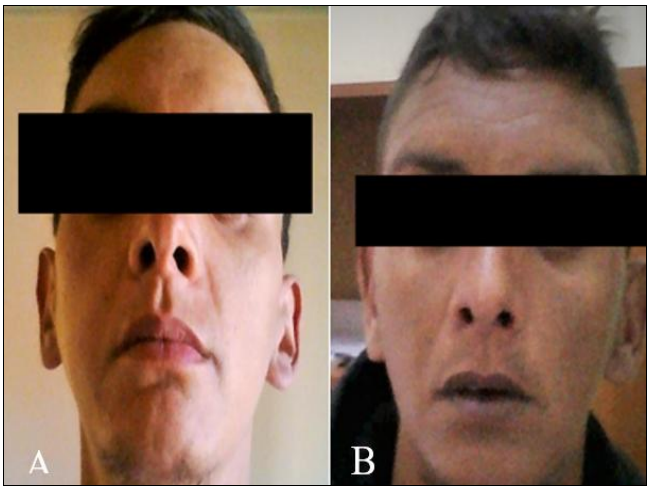


**Fig 1:** Progression of facial hyperpigmentation over 6 months of hemodialysis. Panel A shows the patient's appearance before dialysis initiation, with normal skin color. Panel B shows the same patient 6 months after starting hemodialysis, revealing progressive melanoderma with generalized hyperpigmentation predominantly on sun-exposed areas (face, neck). This striking contrast illustrates the progressive nature of adrenal insufficiency-related hyperpigmentation

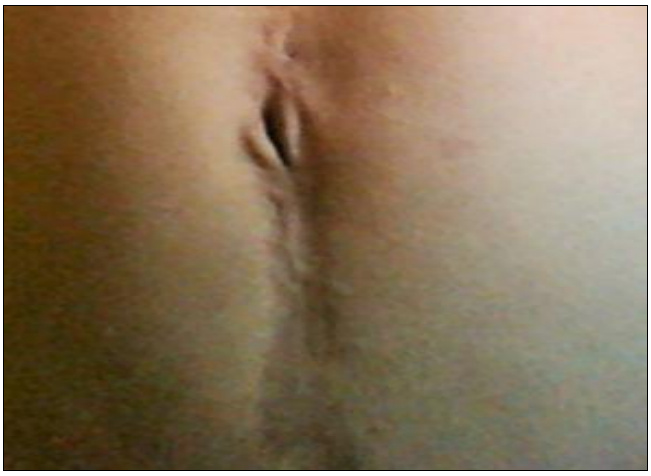

**Fig 2:** Abdominal scar. Scar from previous white peritonitis

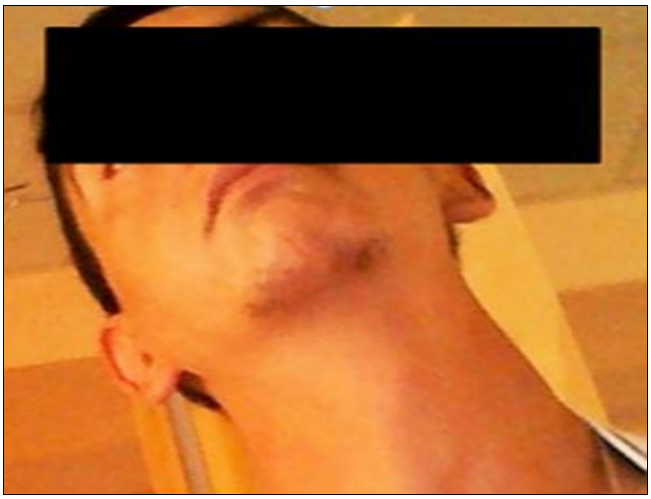

**Fig 3:** Neck scar. Scar from previous goiter surgery

Laboratory investigations confirmed severe hypercalcemia (> 115 mg/L, normal: 85-105 mg/L), hyponatremia (130 mmol/L, normal: 135-145 mmol/L), elevated potassium, and renal failure (urea 2 g/L, creatinine 122 mg/L). Endocrinological evaluation revealed a highly elevated plasma ACTH level at the upper limit of detection, associated with a low serum cortisol level, confirming primary adrenal insufficiency (Addison's disease). An abdominal CT scan revealed bilateral adrenal calcifications (Fig 4).

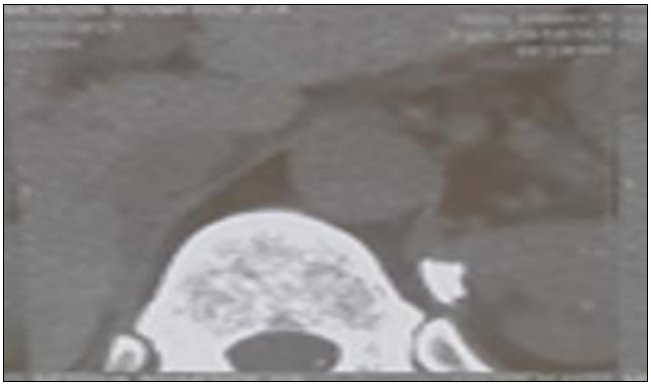

**Fig 4:** Abdominal CT scan showing bilateral adrenal calcifications. Axial CT image demonstrates calcifications of both adrenal glands (arrows), a radiological clue suggestive of adrenal amyloidosis in this context

### 2.3 Etiological Diagnosis

The combination of primary adrenal insufficiency, a childhood history of recurrent fever, and ESRD due to amyloidosis strongly suggested the diagnosis of FMF complicated by AA amyloidosis. A salivary gland biopsy was performed, which confirmed AA amyloidosis with positive Congo red staining showing apple-green birefringence under polarized light and positive anti-AA immunohistochemistry. Serum protein electrophoresis and immunofixation were strictly negative, formally ruling out AL amyloidosis. Finally, genetic testing identified a homozygous M694I mutation in the *MEFV* gene, definitively confirming the diagnosis of FMF.

### 2.4 Therapeutic Management and Outcome

The patient was started on oral hydrocortisone replacement therapy for adrenal insufficiency, with regular biological monitoring. While there was initial clinical improvement, the patient's condition progressively worsened due to advanced, multi-organ AA amyloidosis. He developed severe chronic diarrhea and progressive malnutrition, leading to cachexia. Despite supportive care, he died from complications of severe diarrhea, malnutrition, and sepsis one year after the diagnosis of adrenal insufficiency was made.

## 3. Discussion

We report a rare and instructive case of a patient with FMF and AA amyloidosis whose diagnosis was ultimately revealed by the development of primary adrenal insufficiency. This case is remarkable for several reasons, including the unusual pattern of symptom evolution after starting dialysis, the diagnostic challenges encountered, and the tragic, preventable outcome.

AA amyloidosis is a dreaded complication of FMF, most frequently affecting the kidneys (80% of cases), but it can also involve the liver, spleen, gastrointestinal tract, and heart [1, 4]. Adrenal involvement, however, is exceptional, with only a handful of cases reported in the literature [5, 7]. In most instances, amyloid deposits are discovered incidentally at autopsy. Our observation is particularly original because adrenal insufficiency was the key diagnostic clue that led to the identification of AA amyloidosis as the underlying etiology, in a patient already on dialysis for an undifferentiated amyloid nephropathy. As noted by Gharabaghi *et al*., "involvement of adrenal glands leading to significant inefficiency is rarely seen in FMF patients with amyloidosis" [8].

The evolution of this patient's symptoms provides a crucial clinical lesson. After starting hemodialysis, his typical FMF attacks ceased, only to be replaced two months later by a new, continuous syndrome of fatigue, abdominal pain, and weakness. We hypothesize that this transition was multifactorial. Hemodialysis may have partially cleared inflammatory mediators, temporarily reducing acute attacks. Simultaneously, the progressive deposition of amyloid may have shifted the clinical picture from intermittent inflammation to continuous organ dysfunction. Most importantly, the development of adrenal insufficiency may have blunted the typical febrile inflammatory response, masking the attacks. Clinicians must be alert to this pattern: the disappearance of intermittent FMF flares in a dialysis patient, followed by the emergence of persistent asthenia and abdominal pain, should prompt immediate investigation for adrenal insufficiency. This change in symptomatology is a diagnostic pitfall that can significantly delay recognition and treatment [6, 7].

Several clinical and biological signs were key to the diagnosis in this patient.

**Hypercalcemia:** This was a major clue. In an anuric patient, hypercalcemia is often wrongly attributed to tertiary hyperparathyroidism. However, severe hypercalcemia (> 115 mg/L) is a well-known feature of adrenal insufficiency and should prompt its investigation [5, 6].

**Hyponatremia:** Another common finding, due to cortisol deficiency and increased secretion of antidiuretic hormone (SIADH) [9].

**Intradialytic hypotension:** A hallmark sign of adrenal insufficiency. The diseased kidneys can no longer compensate for aldosterone deficiency, making dialysis patients particularly susceptible [10]. Delanaye and Krzesinski reported a similar case of a 34-year-old dialysis patient with FMF who developed severe intradialytic hypotension and adrenal insufficiency with massive bilateral adrenal calcifications [5].

**Hyperpigmentation (Melanoderma):** This characteristic clinical sign of primary adrenal insufficiency is caused by melanocyte hyperstimulation by ACTH, which shares homology with α-melanocyte-stimulating hormone [11].

**Adrenal Calcifications:** A valuable radiological clue often associated with amyloidosis, but can also be seen in conditions like adrenal hemorrhage, infection (tuberculosis, histoplasmosis), or neoplasms such as myelolipoma or adrenocortical carcinoma [5, 12]. The presence and pattern of calcifications, combined with clinical history, can help narrow the differential diagnosis [12]. Delanaye and Krzesinski reported a similar case of a 34-year-old dialysis patient with FMF who developed adrenal insufficiency with massive bilateral adrenal calcifications [5].

**Chronic Abdominal Pain:** While often attributed to FMF peritonitis, persistent abdominal pain is a classic sign of adrenal insufficiency and should be considered in the differential diagnosis [13]. Gastrointestinal symptoms such as nausea, abdominal pain, and vomiting are particularly common in adrenal insufficiency [13].

The patient's fatal outcome was ultimately driven by gastrointestinal AA amyloidosis, which led to severe chronic diarrhea, malabsorption, and malnutrition. AA amyloidosis can involve the gastrointestinal tract, leading to malabsorption, protein-losing enteropathy, and severe malnutrition [1, 4]. This final chapter of his disease, combined with ESRD and adrenal insufficiency, created a fatal cascade.

### The Preventable Tragedy and Public Health Message

This case represents a tragedy that could have been avoided. FMF is prevalent in Algeria, and AA amyloidosis is effectively preventable with early initiation of colchicine therapy in childhood [14]. When started early and taken consistently, colchicine prevents febrile attacks and the development of amyloidosis [3, 14, 15]. Our patient's FMF was never diagnosed in childhood, and he never received colchicine. By the time a diagnosis was made, irreversible organ damage (ESRD and widespread amyloidosis) had already occurred.

The identification of the homozygous M694I mutation, the most common and most amyloidogenic mutation in the

Algerian population [2], underscores the high genetic risk. This case serves as a stark call to action. We must improve awareness among pediatricians and general practitioners so that children with recurrent febrile episodes are screened for FMF and started on colchicine [14].

**Diagnosis: Lessons Learned**

- **Screening:** In any dialysis patient with severe hypercalcemia, unexplained hypotension, or chronic abdominal pain, adrenal insufficiency must be considered, and simple cortisol and ACTH measurements should be performed [5, 15].
- **A clue:** The presence of adrenal calcifications on CT should raise suspicion for adrenal amyloidosis in a patient with known FMF or AA amyloidosis [5, 12].
- **A safe biopsy:** Salivary gland biopsy is an excellent, safe alternative to renal biopsy for the diagnosis of AA amyloidosis, especially in patients with ESRD [16].
- **A clinical sign:** Hyperpigmentation and chronic abdominal pain are valuable clinical signs that should not be overlooked in patients with suspected adrenal insufficiency [11, 13].

## 4. Limitations

We acknowledge that this is a single case report, and the diagnosis of adrenal AA amyloidosis was not confirmed by direct adrenal biopsy. However, the strong clinical context, the confirmation of systemic AA amyloidosis via salivary gland biopsy, the exclusion of other causes of adrenal insufficiency (no signs of hemorrhage or infection on CT, negative serum immunofixation), and the positive genetic testing for FMF make the diagnosis highly probable.

## 5. Conclusion

We report an exceptional case of primary adrenal insufficiency revealing adrenal AA amyloidosis complicating Familial Mediterranean Fever (homozygous M694I mutation). The clinical picture included chronic abdominal pain, severe hypercalcemia, hyponatremia, intradialytic hypotension, asthenia, muscle weakness, and progressive hyperpigmentation. Abdominal CT scan showed bilateral adrenal calcifications. Salivary gland biopsy confirmed AA amyloidosis, and genetic testing confirmed FMF.

Notably, the patient's typical FMF attacks ceased after dialysis initiation, but a new continuous symptomatology of fatigue and chronic abdominal pain emerged, highlighting the diagnostic challenge of adrenal insufficiency in this context. Despite initiation of hydrocortisone replacement therapy, the patient died one year later from complications of advanced AA amyloidosis, including severe diarrhea and malnutrition.

This case emphasizes the importance of screening for adrenal insufficiency in any dialysis patient presenting with unexplained hypercalcemia, severe intradialytic hypotension, or chronic abdominal pain [5, 6]. Adrenal calcifications should raise suspicion for adrenal amyloidosis in this context [5, 12].

Most importantly, this case underscores a critical public health message: FMF is prevalent in Algeria, and AA amyloidosis and its devastating complications, including end-stage renal disease, can be prevented by early initiation of colchicine therapy at pediatric age [14]. We must remain vigilant and ensure that all children with suspected FMF receive adequate colchicine prophylaxis to prevent this tragic outcome.

**Take-Home Messages**

1. **AA amyloidosis** can involve the adrenal glands and cause adrenal insufficiency. The diagnosis is simple if considered: measure cortisol and ACTH, then perform an abdominal CT scan [5, 6].
2. The **disappearance of typical FMF attacks** after dialysis initiation, followed by new persistent symptoms, should alert clinicians to adrenal insufficiency [6, 7].
3. **FMF is present in Algeria.** Colchicine therapy in childhood prevents AA amyloidosis and end-stage renal disease. We must diagnose and treat FMF early to avoid preventable deaths [14].

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