

CASE REPORT

Hypoadrenal syndrome in a patient with amyloidosis secondary to familial mediterranean fever

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SUMMARY

Amyloidosis is a common complication of poorly controlled familial Mediterranean fever (FMF). A variety of organs including kidneys, heart, liver, thyroid and adrenal glands may be clinically affected. However, involvement of adrenal glands leading to significant inefficiency is rarely seen in FMF patients with amyloidosis. The impairment of neuroendocrine immune system in FMF together with proteinuria in renal amyloidosis is a challenge while interpreting adrenal function tests. Here we present a case report of a 42-year-old man with FMF and renal failure due to amyloidosis whose disease course was complicated by adrenal insufficiency.

BACKGROUND

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory syndrome presenting with recurrent bouts of fever, serosal, synovial or cutaneous inflammation. Although it was first diagnosed among patients of Mediterranean ancestry; it is seen with increasing frequency in other parts of the world. Febrile episodes develop in 90% of patients by the age 20 and the treatment of choice is oral colchicine which not only decreases the intensity of febrile attacks but also prevents the most dreadful complication of disease, systemic amyloidosis. Deposition of fragments of amyloid fibrils, as an acute phase reactant, leads to systemic amyloidosis. The amyloid fibrils deposit in various organs, including kidneys, liver, spleen, intestine, endocrine glands, adrenals and testes. Therefore, patients with long-term poorly controlled disease may present with a variety of symptoms due to multi organ involvement. As a result, nephrotic syndrome and chronic kidney disease is one of the most fearful complications of systemic amyloidosis in uncontrolled FMF. However, clinically significant involvement of other organs such as adrenal glands is rarely reported.^{1 2} Diagnosis of adrenal insufficiency and interpretation of laboratory tests in the context of heavy proteinuria and nephrotic syndrome in FMF may be challenging. Here, we report a case of FMF with end-stage renal disease due to amyloidosis and nephrotic syndrome, admitted to intensive care unit (ICU) with refractory shock that was diagnosed to have concomitant hypoadrenal syndrome. We believe that report of such cases may contribute to the literature on such uncommon complication of FMF.

CASE PRESENTATION

The patient was a 42-year-old man experiencing the constellation of fever, abdominal pain and arthralgia since early childhood. At the age of 31, he underwent appendectomy for an acute episode of fever and abdominal pain. Then after, he was diagnosed to have FMF and treated by daily oral colchicine. Three years later, he developed generalised oedema and histological studies of kidney tissue samples revealed renal amyloidosis. Six months before this recent admission, he developed a bout of sustained abdominal pain, nausea, vomiting, diarrhoea and severe asthenia, which was a few days following injection of influenza and meningococcal vaccines. His condition improved slightly after administration of intravenous rehydration therapy. Similar bouts recurred within the following months, which were attributed to colchicine toxicity, cholecystitis and infectious enteritis. The kidney function deteriorated steadily and abdominal pain, nausea and watery diarrhoea persisted leading to referral for further diagnostic workups at our hospital.

All of his brothers and sisters had FMF too.

INVESTIGATIONS

He was ill, febrile and confused on admission. On physical examination lower extremity pitting oedema was detected. His blood pressure was 90/65 mm Hg on right arm. Blood tests showed normocytic and normochromic anaemia, serum creatine 3.8 mg/dl, total serum protein 3.1 g/dl, while his serum albumin level was 1.2 g/dl. There was no bacterial growth on his multiple blood and urine cultures. Repeated examinations of stool samples revealed non-inflammatory diarrhoea. He also had primary hypothyroidism but bone minerals and parathyroid hormone tests were normal.

There was no sign of cardiac amyloidosis on echocardiographic imaging.

Haemodialysis was performed because of established uremic encephalopathy. Haemodialysis progressed to shock. He was admitted to the ICU. Intravenous crystalloids and norepinephrine were administered. No specific cause such as volume loss, bleeding, sepsisemia, acidemia, electrolyte disturbance or cardiopulmonary disease was found during a thorough diagnostic workup for the vasopressor-responsive shock.

On the basis of the constellation of undetermined hypotension, non-inflammatory diarrhoea and amyloidosis due to FMF, hypoadrenal syndrome due to amyloid fibril deposition was the probable diagnosis.

To cite: Asadi Gharabaghi M, Behdadnia A, Asadi Gharabaghi M, *et al.* *BMJ Case Reports* Published online: [please include Day Month Year] doi:10.1136/bcr-2012-007991

Blood tests showed serum cortisol of 10 µg/dl at the time of ICU admission. Considering serum albumin level, 1.2 g/dl, he probably had a hypoadrenal syndrome. Sixty minutes after intravenous administration of 250 µg tetracosactide, a synthetic adrenocorticotrophic hormone (ACTH) his serum cortisol increased to 14.5 µg/dl. Considering the ambiguity of diagnosis based on adrenal test in patients with hypoproteinemia due to nephrotic syndrome, stress doses of intravenous hydrocortisone were administered and a dramatic response of the blood pressure, following the test confirmed the diagnosis of adrenal insufficiency.

TREATMENT

He was treated by intravenous hydrocortisone 300 mg daily and levothyroxine 50 µg daily. Soon after the administration of hydrocortisone, his blood pressure rose. Hence, the intravenous norepinephrine infusion was discontinued. The diarrhoea and nausea improved significantly, as well. The haemodialysis was continued and he was discharged from ICU to nephrology department for further follow-ups.

OUTCOME AND FOLLOW-UP

Unfortunately, he died a few weeks later due to an overwhelming septicæmia caused by *Streptococcus* D species.

DISCUSSION

Amyloidosis is a common complication in patients with poorly controlled autoinflammatory syndromes such as FMF. It is not uncommon to see amyloid depositions in other organs such as liver, heart, nervous system or adrenal glands once kidneys are involved. However, the prevalence of adrenal insufficiency is not yet understood in patients with amyloidosis due to FMF. Yilmaz *et al*³ showed that the presence of renal amyloidosis in patients with FMF is not necessarily associated with adrenal insufficiency. ACTH stimulation test are used to evaluate adrenal function in FMF patients with or without renal amyloidosis. Unfortunately, the interpretations of adrenal tests are challenging in patients with FMF. It is even more challenging when FMF patients develop amyloidosis-induced nephrotic syndrome because even before development of amyloidosis, the baseline levels of cortisol and ACTH may be compromised, especially during febrile attacks. Topaloğlu *et al*⁴ showed a negative correlation between level of cortisol and interleukin-6(IL-6) during febrile episodes. It seems that there are derangements in neuro-endocrine immune system function in FMF patients notably during acute inflammatory episodes. Sav and colleagues showed that the response of cortisol to ACTH stimulation test depends on the time, the test was performed. In other words, the peak serum cortisol is higher when the patients are evaluated during a febrile attack.⁵ Korkmaz *et al*⁶ evaluated cortisol response to insulin-induced hypoglycaemia in attack-free FMF patients and found that there is a blunted response 30 min after the provocation in FMF group compared to healthy group. However, no significant difference was recorded when the response was evaluated 90 min after the provocation. Therefore, it seems that physicians must be cautious in interpretation of adrenal stimulation tests during FMF attacks. The presence of nephrotic syndrome makes the interpretation of test more complex. Brennan *et al*⁷ reported a case of nephrotic syndrome due to amyloidosis and concurrent hypoadrenal syndrome based on rapid stimulation test. Their patient was a 53-year-old woman whose symptoms did not improve with steroid replacement therapy. She had a 13 g/day proteinuria at first, when she developed end-stage

renal disease and received a renal replacement therapy; cortisol response to rapid stimulation test reverted to normal. The authors believed that the abnormal response on the initial test was attributed to low serum cortisol-binding globulin (CBG) caused by heavy proteinuria. Davidson *et al*⁸ reported a similar case in which subnormal response to ACTH stimulation test was secondary to low level of CBG. CBG is the predominant carrier of cortisol. Thus, heavy proteinuria and urinary loss of CBG may lower the blood level of cortisol, even though the free fraction of cortisol remains constant. As a result of this it is recommended to measure free cortisol, CBG and free cortisol index while attempting to evaluate hypothalamo-adrenal axis in patients with proteinuria. Yet, this issue needs to be addressed by further studies in future. We interpreted the subnormal response of the patient's cortisol to rapid stimulation test as an indication for the presence of hypoadrenal syndrome because he was not admitted during an acute inflammatory attack, and the combination of unexplained shock, nausea and non-inflammatory diarrhoea were suggestive of an adrenal insufficiency. He also had renal amyloidosis and primary hypothyroidism raising the suspicion of multiorgan involvement by amyloid fibrils. The most important diagnostic clue was notable response of hypotension and diarrhoea to steroid replacement therapy.

Learning points

- ▶ Familial Mediterranean fever may be complicated by adrenal insufficiency due to amyloid fibril depositions in adrenal glands.
- ▶ Hypoadrenal syndrome should be considered in evaluation of patients with unexplained hypotension.
- ▶ The interpretation of cortisol response to rapid stimulation tests may be challenging in heavy proteinuria secondary to nephrotic syndrome.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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