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End-stage renal failure due to amyloidosis and recurrent fever on dialysis—is there a link?

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The case

A 57-year-old woman, on dialysis for 6 years because of AA (reactive) amyloidosis (diagnosis based on kidney biopsy), seeks medical attention for malaise, fever (particularly after the dialysis sessions), hypertension and dyspnoea.

At the clinical visit, she is anxious, pale and in obvious stress; her blood pressure is 155/95 mmHg, her pulse rate is 110 bpm; her hypertrophic artero-venous fistula for haemodialysis shows no sign of inflammation. Except for these findings, the examination is unremarkable; in particular, no palpable lymph nodes or skin lesions are noted.

Her recent clinical history is also unremarkable, despite the progressive onset of weakness, which she initially explained as due to a rapid decrease in haemoglobin after the discontinuation of erythropoietin, motivated by a previous level over the target. She concomitantly reported decreased appetite and low-grade fever (37.8–38°C), initially occurring only in the evening after the dialysis session, but subsequently almost every evening. She has no pain or any symptoms, except occasional dyspnoea.

Her first tests are unremarkable: white blood cells are in the normal range, chest X-rays and abdominal ultrasounds fail to show any abnormality. The only abnormality found at the first set of tests is an increased erythrocyte sedimentation rate (45 mm/h) and C-reactive protein (5.5, normal <3 mg/dl); haemocultures repeatedly performed at start and end of dialysis are all negative.

What is your differential diagnosis of the present clinical problem?

What is missing at the clinical visit?

What kind of tests would you perform in this patient?

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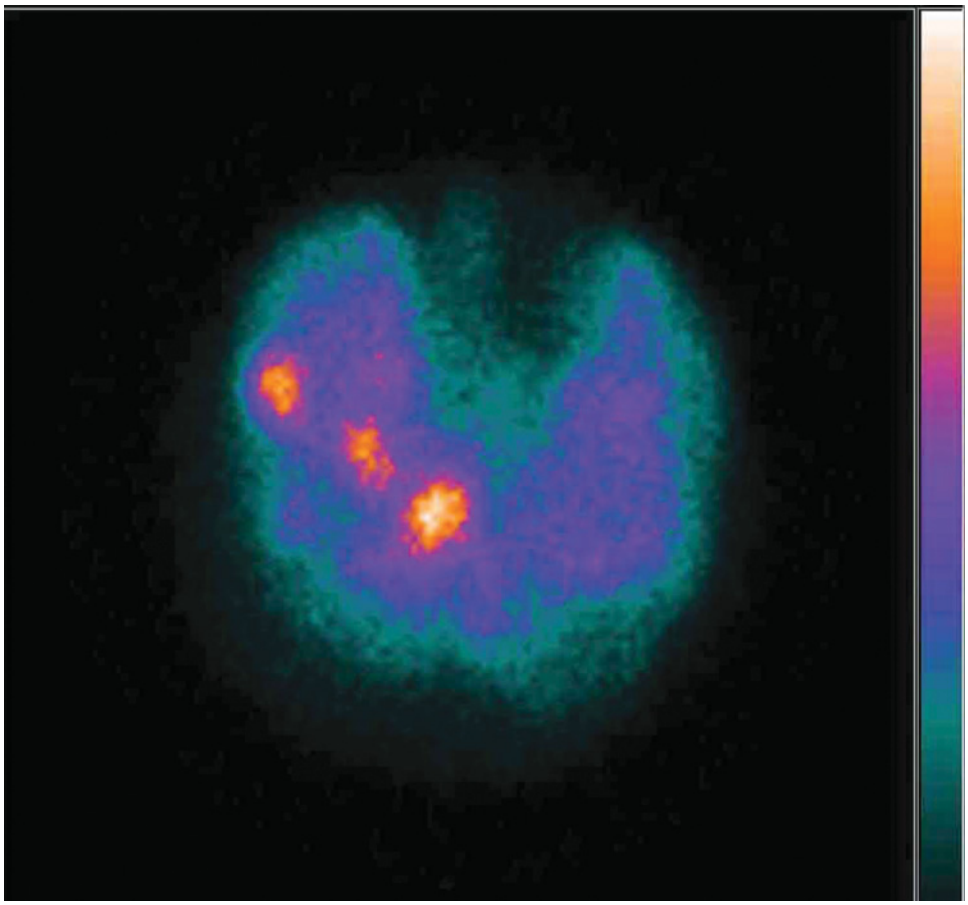

Fig. 1. Thyroid scintiscan showing multiple areas of hyperactivity. Diagnostic of toxic multinodular goitre.

The patient suffers from toxic multinodular goitre.

Thyrotoxicosis is a well-known cause of fever of unknown origin in the general population. However, its incidence in the dialysis population is not estimated and the diagnosis may be challenging in dialysis patients due to the clinical mimicry of uraemia, as will be further discussed.

Before analysing the potential causes of fever of unknown origin (FUO), we tried to identify causes of fever linked with AA amyloidosis. The first hypothesis was familial Mediterranean fever and related genetical diseases. Familial Mediterranean fever was excluded by DNA testing. Furthermore, in our patient, DNA testing to identify mutations known to be associated with other familial forms of amyloidosis with renal involvement in apolipoprotein AI, apolipoprotein AII, fibrinogen, lysozime and transthyretin was negative. Serum amyloid protein A (SAA) was on the contrary persistently over the reference limit (10–17 mg/l, upper reference limit: 6.4 mg/l).

The latter data led us to propose the diagnostic pathways for AA amyloidosis instead of focusing on the current array of signs and symptoms. Reactive amyloidosis (AA) is a rare complication of chronic inflammatory diseases, such as inflammatory arthritides, inflammatory bowel diseases, chronic infections, autoinflammatory syndromes and several neoplasias. The diagnosis of AA amyloidosis is just as challenging as the diagnosis of FUO, with which it shares the main diagnostic categories: infectious, neoplastic, rheumatological, miscellaneous and unknown. Notably, 15–30% of cases still go undiagnosed, in spite of improved diagnostic techniques [1,2]. For the sake of the present report, we should mention that the cause of AA amyloidosis goes unrecognized in at least 5% of the cases, as was the case with our patient [3,4]. In fact, despite several attempts to identify the cause of the amyloidosis, the results were negative for a wide range of tests (the usual routine, plus autoimmunity testing, culture specimens, with particular attention to mycobacterium tuberculosis, total body CT scan and total body scintiscan with radiolabelled white blood cells) both at dialysis start and 3 years later, when she underwent evaluations for kidney transplant wait-listing.

In our patient, at the time of the present report, the correct diagnosis was suggested by the low TSH levels (0.02) recorded at routine TSH testing in the previous month (TSH is controlled twice yearly in our setting). The diagnosis was confirmed at a further control by the marked inhibition of TSH levels (0.0002), with high-thyroid hormone levels.

Thyrotoxicosis is an example of a diagnosis of fever of unknown origin normally based on distinctive clinical features, in which laboratory analyses are usually merely confirmatory [1].

In our patient, this relatively simple differential diagnosis was not initially taken into account, because of the mimicry

of uraemia and her long and partially unresolved clinical history of AA amyloidosis.

Indeed, in a female patient presenting with malaise, tachycardia and anxiety, the hypothesis of thyroid dysfunction is quite obvious. However, in this case, some of the usual hallmarks of hyperthyroidism were attenuated or modified by uraemia. In particular, weight loss was hidden by the lack of renal function and her hypertension was not systolic (as is usual in hyperthyroid states) but systo-diastolic, as the weight loss induced water- and salt-dependent hypertension. The anxiety state is difficult to interpret in a patient with a chronic, long-lasting disease. Anxiety is also very common in dialysis patients on the kidney transplant wait-list and an increase in anxiety can easily be overlooked in the dialysis setting [5]. Our patient had at least two alternative causes of tachycardia (a large hypertrophic AV fistula and anaemia, only partially corrected by the erythropoietin therapy), which hindered the correct interpretation of this symptom.

Missing in her clinical description was the mention of a moderate-sized goitre, a frequent finding (particularly in females) in areas of relative iodine deficiency, as in the present case and thus often overlooked [6–8]. Goitre is also known to be a manifestation of thyroid amyloid deposits in AA amyloidosis and can be associated with hyperthyroidism. However, in our patient this association was not present, as no evidence of amyloid deposit was found in the thyroid of the patient, and SAA levels remain elevated even after thyroidectomy (range 1–3 months after total thyroidectomy 10.4–14 mg/l; upper reference limit: 6.4 mg/l).

Therefore, our patient presented a casual association between a rare disease (AA amyloidosis) and a relatively common one (hyperthyroidism), a potentially misleading association, taking into account the clinical mimicry of uraemia, amyloidosis and thyroid disorders.

She was started on Tapazole therapy, which resulted in a rapid clinical response and normalization of thyroid hormone levels within one month, and underwent total thyroidectomy a few months later. The thyroid scintigraphy in Figure 1 shows toxic multinodular goitre, with two main areas of overfunction.

Within the context of a high prevalence of thyroid function derangements, toxic multinodular goitre is the most common cause of hyperthyroidism above age 55. Thyroid disorders should always be considered in the differential diagnosis of several clinical problems, including fever of unknown origin in dialysis patients, as in the overall non-uraemic population [6–8].

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