JIM Letter to the Editor

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AL amyloidosis, hypothyroidism and reduced tissue availability of thyroid hormones by thyroid hormone-binding immunoglobulin: a new possible perspective

Dear Sir,

We read the interesting article by Muchtar *et al.* [1] on the prevalence of hypothyroidism in AL amyloidosis and its association with survival disadvantage. Particularly, hypothyroid patients had more frequent renal and hepatic involvement by amyloidosis, and a higher light chain burden than euthyroid patients. Uncited in their paper is that primary hypothyroidism is associated with increasing mortality [2], also in renal diseases. We hope to offer the authors a new perspective of viewing and interpreting their data.

We studied amyloidoses, thyroid disorders and autoimmunity, including thyroid hormone (TH) binding immunoglobulins/autoantibodies (THAb). We demonstrated that all known fibrillar amyloid-related proteins (ARP) share local homology, which helps explaining why proteins so diverse genetically and functionally share the property of forming amyloid deposits. The common motif resulting from multiple alignment of ARP was 'D/E/N/Q, A/G, D/E/N/Q, 4-20X, V/I/L/M, D/E/N/Q, R/K/H, 0-6X, V/I/L/M, 0-5X, F/Y/W, 4-5X, D/E/N/Q, 0-2X, R/K/H, 0-12X, A/G, V/I/L/M, 0-3X, V/I/L/M, 0-2X, A/G' [3]. Noteworthy, the ARP transthyretin, apolipoproteins (apoA-I, A-II, A-IV, E) and immunoglobulins also share TH binding, a property that should be linked to a 5-residue motif originally discovered in apolipoproteins. As confirmed in our work on human and animal TH plasma binding proteins, in the perfect version of the motif, the first position is occupied by F, Y or W, the second and fifth by I, L, M or V, the third and fourth by any amino acid. However, imperfect versions exist, even within the same protein. For instance, within or adjacent to the amyloid motif, the perfect and imperfect version of the 5-residue motif of human apoA-I are **YV**DV**L** and **YV**SQF, whilst human apoA-II contains three imperfect versions (**Y**FQT**V**, **Y**GKD**L**, **Y**FVE**L**). For Ig lambda (accession code P01699), the TH binding motifs are **W**AQS**V** and **W**YQQ**L**; for Ig kappa (accession code 3DVF_A), they are **F**TFT**I** and **YL**PQT, plus many others in segments published in the literature (**YL**AWY, **F**TLT**I**, **Y**YTT**L**, **WL**AWY, **F**TLT**I**, **YV**NWY, **FL**IYD, **F**TFT**I**, **FI**FPP, **Y**ACE**V)**. Because of reference to diabetic nephropathy in our Letter (see below), it is noteworthy that Cogné *et al.* allude to similarities between glomerular lesions of light chain deposition disease and diabetic nephropathy.

THAb are autoAb to iodinated epitopes of thyroglobulin (Tg), *viz.* Tg regions containing iodinated tyrosines. Because some tyrosines are T3-hormonogenic, some are T4-hormonogenic and others are both T3- and T4-hormonogenic, THAb binding only T3, only T4, or both T3 and T4 may be synthesized. IgM and IgG THAb are detectable in serum, as first shown in a patient with Waldenstrom's macroglobulinemia and with hypothyroidism that had no explanations other than the high TH binding capacity of THAb. Interestingly, THAb abnormally bound also serum cortisol.

THAb are rare in the general population (<1%), but relatively frequent (>20%) in autoimmune thyroid diseases (AITD) and both autoimmune and nonautoimmune nonthyroid diseases (NAINTD) [4,5]. Amongst NAINTD, there are Waldenstrom's macroglobulinemia and other haematologic malignancies including one cause of AL amyloidosis: multiple myeloma (MM) [5].

In a study on 82 patients with haematologic malignancies (MM, $n = 22$, non-Hodgkin lymphoma [NHL], $n = 36$; chronic lymphocytic leukaemia [CLL], $n = 4$; chronic myeloid leukaemia [CML], $n = 8$; polycythemia vera [PV], $n = 12$) and 104 controls matched for demographic characteristics, the following ultrasonographic data were found [6]. Enlarged thyroid (goitre) was detected only in patients with MM (10%) or PV (17%). The rate of thyroid nodules was the highest in MM and PV, and patients with MM had the largest thyroid nodules. Sonographic signs of thyroiditis were detected only in MM (10%) and NHL (13%). In another study on the same patients and controls [5], 13% of patients and 1% of controls ($P = 0.0006$) were THAb positive. THAbs were observed in four malignancies (MM=3/

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22, NHL=5/36, CLL=1/4, CML=2/8, PV=0/12). In most cases, a single type was detected (one class, one hormone), with T3-IgG predominating. T3-IgM and T4-IgG were identified only in patients with NHL and CML, respectively. MM was the only malignancy where we found T4-IgM, alone or associated with T4-IgG. Although all 22 patients with MM were thyroglobulin Ab (TgAb) and thyroperoxidase Ab (TPOAb) negative, two (9.1%) had ultrasonographic signs of thyroiditis and were THAb positive. The other malignancy with ultrasonographically detected thyroiditis was NHL (5/36), and these five patients also were THAb positive. THAb positivity with thyroiditis and undetectable TgAb and TPOAb was observed in other patients with AITD or NAINTD [4]. Thus, THAb are a marker of early thyroid damage.

THAb were also associated with renal amyloidosis. In experimental animals, thyroiditis and THAb are induced by immunization with Tg, with serum THAb being measurable in early stages of thyroiditis. In rabbits and guinea pigs immunized against Tg and with circulating THAb, lesions were noted in the thyroid and other tissues, including kidneys. Amongst these lesions, lymphocytic thyroiditis, vasculopathies and amyloidosis were remarkable. Concerning thyroid and renal amyloidosis, it was concluded that the congophilic hyaline deposits represent AL amyloid. At autopsy, the thyroid tissue of a hypothyroid patient with THAb contained broad bands of hyalinized connective tissue. Those lesions may cause '*inhibition of free diffusion of thyroid hormone across the vascular wall, which could then result in pockets of focal hypothyroidism although the circulating thyroid hormones may be normal.*' [7]. Livshits *et al.* found a significantly greater rate of T4-THAb amongst 21 patients with coronary atherosclerosis than in 10 healthy controls with comparable levels of immunoglobulins and immunoglobulin classes. Finally, in 52 patients with type 1 diabetes mellitus who were followed up for 6 years, the presence of AITD at baseline was associated with subsequent development of macroangiopathy (0% at baseline versus 33% at follow-up, $P = 0.029$) [4]. These patients had a high prevalence of THAb (92.3% at baseline, 80.7% 6 years later), even when omitting patients with concurrent AITD (88.2% and 87.5%, respectively). Some THAb patterns were associated with progression and development of diabetes-related complications. A 'dangerous' THAb category was T4-IgM, associated with high rates of retinopathy (67%), nephropathy (50%) and neuropathy (33%). Another 'dangerous' THAb category was T3-IgG. Indeed, in addition to future macroangiopathy, there is the risk of future retinopathy, nephropathy or neuropathy [4].

Muchtar *et al.* [1] conclude that '*Evaluation of thyroid function in newly diagnosed AL amyloidosis patients should be routinely performed.*' We think that evaluation should be broadened to thyroid autoimmune status, including THAb. S.B. is ready to collaborate and assay the THAb panel throughout the follow-up of this robust cohort of patients with AL amyloidosis.

Conflict of interest statement

The authors have no conflict of interest to disclose.

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