Editorial

Intestinal presentation of systemic amyloidosis

Amandine Berner[1], Jacques Serratrice[1], Matteo Coen[1,2]^

[1]Service of General Internal Medicine, Department of Medicine, Geneva University Hospitals, Geneva, Switzerland; [2]Unit of Development and Research in Medical Education, Faculty of Medicine, University of Geneva, Geneva, Switzerland

Correspondence to: Matteo Coen, MD, PhD. Service of Internal Medicine, Department of Medicine, Geneva University Hospitals, Geneva, Switzerland; Unit of Development and Research in Medical Education (UDREM), Faculty of Medicine, University of Geneva, Geneva, Switzerland. Email: matteo.coen@hcuge.ch.

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Amyloidosis is a protein misfolding disorder characterized by the deposition of highly stable, insoluble, extracellular, 8–12 nm rigid and non-branching protein filaments: the amyloid protein (from the Greek word *ἄμυλον*, amylon, "starch"; because of amyloid's avidity to take up iodine, as starch does) (1,2). This term was coined in 1838 by the German Botanist Matthias Schleiden but was introduced in human medicine in 1854 by Rudolph Virchow. In his "*Über eine in Gehirn und Rückenmark des Menschen aufgefundene Substanz mit der chemischen Reaction der Cellulose*" (i.e., "About a substance found in the human brain and spinal cord with the chemical reaction of cellulose") (Virchow, 1854) the German pathologist described that the *corpora amylacea* of the nervous system, first described by Purkinje in 1837, stained with iodine like plant starch (3,4). Nevertheless, the first likely illustration of amyloidosis is much more ancient: in 1639, Nicholaus Fontanus (Nicolao Fontano, Nicolaas Fonteyn) first described what could have been a sago spleen (3).

Numerous proteins of different molecular natures can be at the origin of an amyloid deposit (i.e., amyloidogenic), either localized or systemic. Forty-two different amyloidogenic proteins have been identified; 14 appear as systemic deposits, 24 as local deposits, and 4 can appear as both types (5). Iatrogenic (drug-induced) amyloidosis has also been described. To date, four drugs have been shown to induce cutaneous amyloid deposits as a result of repeated local injection; they are insulin (AIns; responsible for the "insulin ball", or amyloidoma), enfuvirtide (AEnf) (6), the glucagon-like peptide 1 analog liraglutide (AGLP1) (7), and the interleukin-1 receptor antagonist protein (AIL1RAP) (8).

The amyloidogenic fibril protein precursors are named after their precursors in abbreviated form (e.g., TTR, transthyretin), preceded by the letter A for amyloid. Instead, to define the name of the amyloidosis type or amyloidosis organ damage, one should use the protein name followed by "amyloidosis" (e.g., ATTR amyloidosis) or by the name of the organ/system involved (e.g., ATTR cardiomyopathy, ATTR-CM or ATTR polyneuropathy, ATTR-PN) (5).

In localized forms (localized amyloidosis), amyloid deposits localize to the site of production of the misfolded protein, often resulting in a tissue mass (hence the name amyloid tumor). The symptoms may vary depending on lesion localization (mass effect) and protein type (9). Cerebral amyloidosis due to Aβ (β protein precursor) is the most frequent type of localized amyloidosis; other typical localizations are the pancreatic islets (deposition of the islet amyloid polypeptide, AIAPP), the seminal vesicles (deposition of the semenogelin, ASem1) and the pituitary gland (deposition of the prolactin, APro) to name a few (10).

In systemic forms (systemic amyloidosis), the

^ ORCID: 0000-0002-6156-1691.

amyloidogenic proteins are expressed at one site. They are subsequently distributed via the bloodstream to reach the different tissue and organs, where they deposit as amyloid fibrils. Systemic amyloidosis can be either acquired or hereditary. Acquired amyloidosis brings together several types of systemic amyloidosis; four are the most frequent types. Amyloid-Light chain amyloidosis (AL amyloidosis) derives from immunoglobulin (Ig) light chain deposits associated with clonal plasma cell proliferation. Beta-2 microglobulin amyloidosis is most often dialysis-related. Systemic amyloid A (AA) amyloidosis (inflammatory) is due to the deposition of the acute phase protein serum amyloid A (SAA). Wild-type (senile) TTR amyloidosis (ATTRwt) is due to an age-dependent reduction in the efficacy of the quality control mechanisms of protein folding, finally leading TTR to become amyloidogenic (2).

Although hereditary amyloidosis is rarer than acquired, it still accounts for approximately 10% of all systemic amyloidoses and is likely to be underdiagnosed. Among the different forms, ATTRv (v for variant) amyloidosis is the most common hereditary amyloidosis worldwide, whereas AFib amyloidosis, in which the amyloidogenic protein is a fibrinogen variant, is common in Europe.

A reliable diagnosis of amyloidosis requires the biopsy of an affected organ or tissue, followed by Congo red stain. Typically, the red-stained amyloid samples demonstrate birefringence under polarized light (commonly, but wrongly defined as "apple-green" birefringence) (11). Beyond histology, immunohistochemistry, immunoelectron microscopy, or mass spectrometry are needed to determine the nature of the protein involved in the amyloid process. An accurate and correct diagnosis of the amyloid type is crucial for disease management (12).

Cardiac amyloidosis is an exception since various non-invasive diagnostic tests are available and accepted to support the diagnosis of cardiac involvement. Nevertheless, only the diagnosis of ATTR cardiac amyloidosis can be made without endomyocardial biopsy, in the presence of the following criteria: typical echocardiographic/cardiac magnetic resonance findings, grade 2 or 3 myocardial uptake (i.e., equal to/greater than bone uptake) on cardiac scintigraphy [99mTc-pyrophosphate (PYP), 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) or 99mTc-hydroxymethylene diphosphonate (HMDP)], and exclusion of clonal cell population producing amyloidogenic Igs (by all the following tests: serum free light chain assay, serum and urine protein electrophoresis with immunofixation) (13).

Gastrointestinal involvement in systemic amyloidosis is not unusual. In 1968, Gilat and Spiro's autopsy study of patients with systemic amyloidosis showed that amyloid deposition within the gastrointestinal tract was frequently found (in 68 of 70 autopsy cases). The authors distinguished two different patterns of amyloid deposition: within the muscle layer of the intestinal wall in primary amyloidosis and in the mucosa in secondary amyloidosis. In all cases, amyloid deposits could be found within the vascular walls of blood vessels. Although patients are often asymptomatic, widespread dysfunction may still occur (14).

Gastrointestinal involvement represents a real diagnostic challenge since clinical manifestations (chronic diarrhea, weight loss, malabsorption, bleeding, dysmotility, pseudo-obstruction, perforation, and amyloidomas-tumor-like lesions) and endoscopic findings are not specific. Amyloidosis can thus mimics other affections of the digestive tract, like inflammatory bowel disease (IBD), cancer, and ischemic colitis (15). It should be kept in mind that in systemic amyloidosis the gastrointestinal tract can be affected early in the presymptomatic phases of the disease. Not only gastrointestinal involvement of amyloidosis can mimic IBD but secondary amyloidosis is a rare but serious complication of IBD (16).

We also have recently described a patient presenting diarrhea, dysphagia, and weight loss due to gastrointestinal involvement of AA amyloidosis in the context of a long-standing Waldenström macroglobulinemia with monoclonal IgM-kappa (κ)-type paraprotein (17).

Wang and colleagues reported (18) the case of a patient with systemic AL amyloidosis with colonic involvement and, to a lesser extent, kidney involvement. Their paper depicts the difficulties of diagnosing systemic amyloidosis in a patient with no history of amyloidosis who displays unexplained gastrointestinal symptoms. A particular concern is the diagnostic delay between symptoms onset, diagnosis, and treatment (more than a year in Wang's patients).

Therefore, a high degree of clinical suspicion must be kept since prognosis of amyloidosis worsens with time, with late-stage disease characterized by progressive multi-organ dysfunction. Moreover, diagnostic delay restricts treatment interventions and patient outcomes mainly depend on the early initiation of therapy.

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Footnote

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