Clinical Case Report

Gastrointestinal ALκ amyloidosis presenting as protein-losing enteropathy correctly diagnosed by immunohistochemistry using amyloid-type-specific antibodies

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ABSTRACT
A 54-year-old man presented with protein-losing enteropathy. Biopsies from the stomach, duodenum, ileum and colon showed deposits of amyloid. The bone marrow showed plasmacytosis. After an initial misdiagnosis of AA amyloid, a revised diagnosis of ALκ amyloidosis was made at an expert referral laboratory. Care must be taken in the use of antibodies and proper controls in the performance and interpretation of immunohistochemistry for amyloidosis. A wide panel of amyloid-type-specific antibodies must be used and interpreted in comparative mode to avoid misdiagnosis.


INTRODUCTION
We report a patient who presented with protein-losing enteropathy due to multiple myeloma-associated amyloidosis that we diagnosed correctly, after an initial misdiagnosis.

THE CASE
A 54-year-old man presented with abdominal pain, altered bowel habits and loss of weight (9 kg in 1 year). On examination, he had pitting pedal oedema and hepatomegaly. Abdominal ultrasonography showed features suggestive of a thickened terminal ileum; barium meal follow-through was suggestive of ileal thickening. Investigations showed proteinuria (256 mg/24 hours, reference 0–150), serum albumin 19 g/L (reference 35–52 g/L), serum globulin 32 g/L (25–31) and D-xylose test revealed malabsorption (<10%). Investigative workup revealed hemoglobin 150), serum albumin 19 g/L (reference 35–52 g/L), serum globulin 32 g/L (25–31) and D-xylose test revealed malabsorption (<10%).

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The clinical and endoscopic diagnosis was Crohn’s disease. Gastric, duodenal, ileal and colonic biopsies revealed ulcerated epithelium with massive deposits of amorphous, and almost acellular eosinophilic material in the lamina propria, submucosa and muscularis propria. Congo red stained this material (Fig. 1a, 1b) and showed apple-green birefringence in polarizer light proving the presence of amyloid (Fig. 1c). The first immunohistochemistry for AA (Dako, dilution 1:1000), for κ and λ light chain (Dako, prediluted) were strongly positive in all three. A bone marrow aspirate and trephine biopsy showed plasmacytosis. Immunohistochemistry on bone marrow biopsy for both light chains expressed κ light chain restriction. Serum protein electrophoresis showed M-band with κ light chain restriction on immunofixation. There were lytic lesions in the D 5, 6 vertebra and calvaria. We made a diagnosis of multiple myeloma, IgGκ type. Because of the diagnosis of apparent AA amyloid in the gastrointestinal biopsy, we looked for any associated aetiology. However, an extensive search for other diseases was unsuccessful. The patient died at home one month later, before treatment could be initiated.

Because of Occam’s razor, which states that plurality must not be posited without necessity, we considered the possibility that we had made an error and that the patient had only one type of amyloid, rather than two. The case was then reviewed by an expert laboratory using immunohistochemistry with a panel of amyloid-type-specific antibodies directed against AA, ALκ, ALλ, ATTR, AβM, fibrinogen, and apolipoprotein A1 (amYmed dilutions 1:800–1:2000, with the PAP-method, respectively). Proper negative and positive antigen and antibody controls were as expected. Only anti-ALκ stained positive (Fig. 1e); the lack of reactivity of all other antibodies excluded the other amyloid types including AA and ALλ (Fig. 1d, 1f). We made a revised diagnosis of ALκ-type amyloidosis.

DISCUSSION
The causes of protein-losing enteropathy include Crohn disease, connective tissue disorders, tuberculosis and amyloidosis. There are more than 25 types of amyloid, of which AL, ATTR and AA are the most common. Appropriate classification of the amyloid is essential because therapy is dependent upon the specific amyloid type and its syndromes. AA amyloid is secondary to inflammatory disorders such as rheumatoid arthritis, Crohn disease and familial Mediterranean fever while AL is seen in monoclonal gammopathy including multiple myeloma. While most patients with AL amyloid have plasma cell dyscrasia, the converse is not true: only about 15% of patients with multiple myeloma develop amyloidosis. Yokose et al have reported a patient who too had protein-losing gastroenteropathy as a presentation of multiple myeloma. The presence of two different amyloid types is rare and has been excluded here.

Misdiagnosis of the specific type of amyloid can occur because of using erroneous techniques, particularly using inappropriate antibodies and/or interpretation of immunohistochemistry. The errors for false-positive cases in typing of amyloid could either be due to the lack of appropriate antibodies or inappropriate immunohistochemical techniques including standardization of reagents, suboptimal processing of tissue or misinterpretation by the pathologist. A thorough investigation would involve a panel
of appropriate amyloid-type-specific antibodies rather than any single antibody. Due to the use of low-quality antibodies, a specific diagnosis may be missed by false-negative result in ALβ and ALκ amyloidosis. The non-reactivity with antibodies directed against native light chains can occur since the amyloid has a different conformation. Other antibodies that are raised against the constant region of light chain may not react when the truncated variable region contains only minor amounts of constant regions. Mass spectrometry has been used to classify amyloid; however, a recent study of blinded comparison of immunohistochemistry using amyloid-type-specific antibodies with mass spectrometry revealed significantly higher sensitivity of immunohistochemistry as compared to mass spectrometry while the specificity did not show a statistical difference.

Our patient had ALκ amyloidosis associated with multiple myeloma because of the clear immunohistochemical results. In addition, this diagnosis is consistent with the clinical presentation. Therefore, the first pathological diagnosis was revised. Our initial error was due to an inappropriate immunohistochemical technique of typing of amyloid resulting in probably overstaining.

Amyloidosis must be considered in the differential diagnosis of the aetiology of protein-losing enteropathy, especially if there are multiple foci of pathology in the gastrointestinal tract. Amyloid must be appropriately typed and the aetiology determined. Finally, when immunohistochemistry is inconclusive or appears misleading, it is worthwhile confirming the diagnosis with an expert. Not doing so may lead to an error in diagnosis and management.

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REFERENCES