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Case Report

Acute cholecystitis with wild-type transthyretin systemic amyloidosis in the gallbladder: a case report

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ABSTRACT

Amyloidosis is a rare disease involving the deposition of organised insoluble proteins in various body viscera, with the disease further classified into different subtypes. In exceedingly rare cases the literature has reported the presence of amyloid deposition in the gallbladder. We described the first documented case of wild-type transthyretin systemic amyloidosis involving the gallbladder, occurring in a 91-year-old female who presented with acute cholecystitis.

Keywords: Amyloidosis, Acute cholecystitis, Gallbladder, Wild-type transthyretin amyloidosis

INTRODUCTION

Amyloidosis is a rare disease referring to the extracellular tissue deposition of organised insoluble fibrillar proteins. Amyloid deposition may result in different clinical manifestations, depending on the type of protein, location of deposition of total quantity of amyloid. The pathogenesis relates to normal, previously soluble precursor peptides undergoing structural changes which subsequently congregate into twisted fibrils and become insoluble. Amyloidosis is classified into localised and systemic categories, depending on the site of precursor production.

A total of 18 systemic and 28 localised forms of amyloidosis have been identified, including four precursor proteins capable of generating deposits in both localised and systemic presentations.[1] The main systemic categories observed in tertiary referral centres and inpatient medical facilities comprise the primary type [immunoglobulin light chain (AL)] and transthyretin (ATTR) types. Nevertheless, various other forms of amyloid, such as the secondary type (AA), are also clinically important.[2]

We described the first documented case of wild-type transthyretin systemic amyloidosis involving the gallbladder, found on histopathology subsequent to an initial presentation of gallstone pancreatitis. Whilst amyloid deposits are commonly found in the kidneys, heart, nervous system, hepatosplenic, intestinal tracts and bone marrow, it is rare for amyloid to localise in the gallbladder. Cases of amyloidosis involving the gallbladder in the literature have additionally been reviewed.[1]

CASE REPORT

A 91-year-old female presented to the emergency department with a one-day history of worsening epigastric pain with associated nausea and vomiting. She reported no changes in her bowel habits and denied symptoms of prutitis. The patient had a background history of osteoporosis and hypertension but was otherwise an independent woman living alone with additional support from her family. She had no known history of previous intraabdominal pathology or surgeries.

At the time of presentation, she was afebrile and comfortable at rest and without features of jaundice. Haemodynamics were stable. Physical examination found a soft and non-distended abdomen with focal epigastric and right upper quadrant abdominal tenderness with a negative Murphy's sign. Laboratory tests showed elevations in lipase and bilirubin of 3127 u/l and 46 µmol/l respectively. Liver function tests showed a mixed derangement with a severe obstructive picture. Further investigations with a computed tomography (CT) scan demonstrated features of chronic gallbladder wall thickening with the presence of multiple gallstones, as well as the presence of early but widespread duct dilatation throughout the pancreas. Cystic lesions within the pancreas were suggestive of side branch focal intraductal papillary mucinous neoplasms (IPMN). Considering her clinical presentation and investigation findings, she was diagnosed as a mild-to-moderate gallstone acute pancreatitis.

The patient had an uneventful admission where her acute pancreatitis was managed conservatively with symptom resolution and resumption of diet within 4 days. An MRI cholangiopancreatography was attempted but not performed due to the patient's claustrophobia. She was discharged home with the aim to perform an elective outpatient cholecystectomy. The patient returned 6 months later and proceeded with an uneventful elective laparoscopic cholecystectomy and she was discharged home 2 days post operatively.

Histopathology yielded unusual findings, showing amorphous eosinophilic material deposition in the vessel walls of the gallbladder, consistent with amyloidosis (Figure 1).

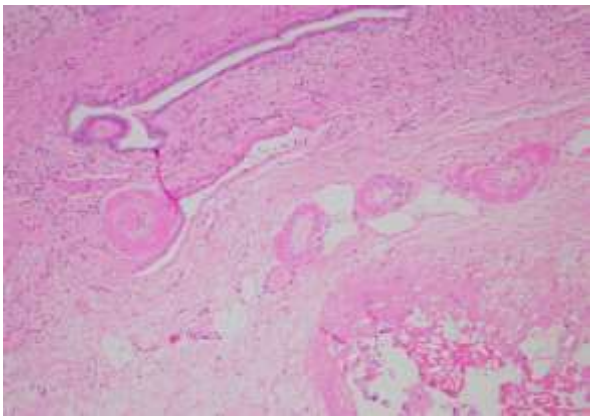

Figure 1: H and E section showing the deposition of eosinophilic material in the vessel walls (at 100X).

Further analysis showed features of apple-green birefringence under polarised light on Congo red staining (Figure 2), persisting after potassium permanganate treatment, suggestive of a non-AA type amyloidosis. Amyloid deposits were positive for amyloid P and transthyretin, while negative for amyloid A. There was additionally weak and nonspecific staining for Kappa and Lambda immunoglobulin light chains on immunohistochemistry. With this information, it confirms a diagnosis of wild-type transthyretin systemic amyloidosis, previously known as systemic senile amyloidosis. Given her advanced age, the patient opted to avoid further complex or invasive investigation for the condition, and of note at 6 months of follow-up remained well and asymptomatic with regard to her amyloidosis. She returned to independent living at home.

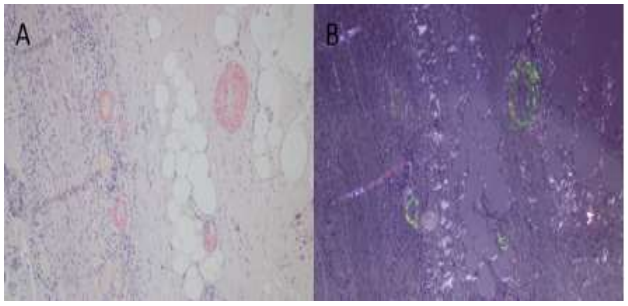

Figure 2: Congo red stain confirming the presence of amyloid (A) brick red colour under normal light; and (B) apple-green birefringent under polarised light (at 100X).

DISCUSSION

Amyloidosis is a rare, progressive and incurable metabolic disease, stemming from the extracellular buildup of abnormal insoluble proteins that can affect multiple organs.[1] This condition is usually classified as systemic or localised, often involving the kidneys, heart, spleen, joints, skin, and digestive tract in the deposition of amyloid, with extremely rare occurrences in the gallbladder. Systemic amyloidosis is further divided into several types, including light-chain (AL or primary), amyloid A (AA or secondary), dialysis-related, hereditary, and wild-type transthyretin amyloidosis.[3,4]

Transthyretin (TTR) amyloidosis relates to the progressive deposition of abnormal TTR protein in organs, resulting from failure of homeostatic mechanisms in wild-type ATTR amyloidosis (ATTRwt) or destabilising mutations in variant ATTR (ATTRv) amyloidosis.[5,6] ATTRwt more specifically refers to the deposition of otherwise normal (wild-type) transthyretin (TTR) in myocardium and other sites; a condition previously known as systemic senile amyloidosis (SSA).[7,8] In both settings, disease occurs as amyloid fibrils aggregate within the extracellular space, causing disruption to the structure, integrity, and functionality of the affected tissue. In the clinical setting, ATTRwt amyloidosis primarily presents itself as cardiomyopathy known as transthyretin cardiac amyloidosis (ATTR-CA), whilst ATTRv amyloidosis is commonly linked with polyneuropathy (ATTR-PN) alongside cardiomyopathy.[9]

Current literature estimates systemic AL amyloidosis to be the most common form of amyloidosis, accounting for 56

percent of all cases whilst ATTR and AA account for 21 and 8 percent respectively.[2]

A review of the PubMed database noted in particular a compilation of 14 published cases of amyloidosis in the gallbladder by Matsuda et al in 2019, as well as two further reports subsequent to this, making 16 cases of cholecystitis with findings of amyloidosis in total.[10-12] Of the 16 cases, over half (56%) were cases of acalculous cholecystitis; remarkably high in comparison to the overall quoted rates in the literature (2-15%).[13] Two theories currently exist relating to the correlation between gallbladder amyloidosis and acute cholecystitis. The first suggests amyloid deposition around the local vasculature, predisposing patients to ischaemic necrosis of the gallbladder. The second suggests amyloid deposition in the gallbladder wall itself to affect normal contractility, and thus subsequent chemical irritation from bile stasis leads to cholecystitis.[10] Factors contributing to our patient developing cholecystitis may be a combination of cholelithiasis as well as localised ischaemia from amyloid deposition in the vessel walls of the gallbladder.

CONCLUSION

This case describes the first published case of wild-type transthyretin amyloidosis involving the gallbladder, contributing further to our understanding of amyloidosis as a disease process. Whilst rare, this case suggests an uncommon aetiology which can predispose patients to common surgical presentations.

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