Reviews

Intestinal amyloidosis: Clinical manifestations and diagnostic challenge

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Abstract

Amyloidosis is a heterogeneous group of diseases in which the extracellular deposition of abnormal fibrillar proteins disrupts tissue structure and function. Intestinal involvement is a very rare manifestation of amyloidosis compared to the most affected organs, the heart and kidneys. Damage of the gastrointestinal tract may be the only manifestation of amyloidosis, or – more often – is a component of the involvement of several organs in systemic amyloidosis. Any part of the digestive tract can be involved; however, the small bowel is the most affected part, followed by the colon. Intestinal amyloidosis is characterized by a heterogeneous clinical picture, with weight loss, chronic diarrhea, abdominal pain, intestinal bleeding, or pseudo-obstruction. Endoscopic findings are characterized by a fine granular appearance, erosions, ulcerations, mucosal friability, multiple protrusions, or tumor-like lesions. Pathologic examination allows for a definitive diagnosis using Congo red staining and a positive sample with apple-green birefringence. The disease can easily be misdiagnosed with several other diseases of the digestive tract and lead to diagnostic challenges in clinical practice. Further, the amyloid colonic deposition may mimic inflammatory bowel disease, malignancy, ischemic colitis, and collagenous colitis. Therefore, gastroenterologists need to include amyloidosis in their diagnostic work-up.

Key words: differential diagnosis, symptoms, intestinal amyloidosis

Introduction

Amyloidosis is a heterogeneous group of diseases, characterized by the extracellular deposition of different abnormal fibrillar proteins, which disrupt tissue structure and function. Amyloidosis can either be acquired or hereditary, systemic or localized. The most affected organs include the kidneys, heart, nervous system, or gastrointestinal tract. The current recommended terminology of amyloidosis, represented in the classification of the International Society of Amyloidosis, is based on the structure of the chemical precursors of the amyloid fibril deposits.[1] While many proteins have the potential to form amyloid fibrils, the most frequent is the immunoglobulin light chain (AL amyloidosis), transthyretin amyloidosis (ATTR), serum amyloid A (AA amyloidosis), and Aβ2 amyloid (hemodialysis – associated amyloidosis).[2–4]

The AL amyloidosis is a malignant condition in which monoclonal immunoglobulin light chains, lambda or less commonly kappa, are produced by a relatively small population of plasma cell clones in the bone marrow. These monoclonal immunoglobulin light chains are deposited extracellularly in the form of misfolded, insoluble protein-complexes known as amyloid.[2] The AL amyloidosis is the most common type of amyloidosis, with an estimated annual incidence of 10–12 cases per million people. The median age of the patients diagnosed with AL amyloidosis was 63 years.[5] The clinical presentation of AL amyloidosis depends on the type and number of organs affected. The heart and the kidneys are affected most, followed by the autonomic nervous system, liver and gastrointestinal tract. The plasma cell clones in AL amyloidosis share phenotypic alterations with those observed in multiple myeloma clones.[2,5] Another type of amyloidosis, AA amyloidosis, is associated with infectious, neoplastic or inflammatory disorders, among which rheumatoid arthritis is one of the most commonly observed. The amyloidogenic fibrils are composed of serum amyloid A protein (SAA) which are hepatic acute phase reactants.[6] Transthyretin amyloidosis (ATTR), a less common type of amyloidosis, is a hereditary disease caused by a transthyretin gene mutation or is acquired as an amyloid disease in the elderly.[7]

Gastrointestinal tract-specific damage may be the only manifestation of the disease, or – more often – is a component of the involvement of several organs in systemic amyloidosis. The digestive tract is affected in 3–28% of diagnosed patients, apart from cardiac, renal or neurological injuries.[8–10] Most types of amyloidosis may be manifested with intestinal involvement without any specific endoscopic characteristics. According to published data, AL amyloidosis is the most diagnosed form of amyloidosis based on gastrointestinal biopsies (52.8–83.3%), followed by AA (1.5–16.2%) and ATTR amyloidosis (4.2–12.5%).[9,11,12]

Intestinal amyloidosis can be easily misdiagnosed and confused with several other digestive tract diseases, and can introduce diagnostic challenges in clinical practice.

The deposition of amyloid within the colon mimics other diseases, such as inflammatory bowel disease (IBD), malignancy, ischemic colitis, or collagenous colitis.[9,10] The misdiagnosis rate of amyloidosis is high because its clinical manifestations are complex and lack specificity. These obstacles often result in a delay of diagnosis and a deleterious effect for patients. The clinical manifestations of intestinal amyloidosis may vary from asymptomatic to serious forms, including intestinal mass or spontaneous perforation. Patients typically present with weakness, fatigue and unintentional weight loss. Moreover, they suffer from abdominal pain, early satiety, nausea, vomiting, diarrhea, fecal incontinence, constipation, and gastrointestinal bleeding.[13,14] Therefore, it is important that both general practitioners (GPs) and gastroenterologists need to include amyloidosis in their diagnostic workup for disease confirmation and more effective treatment.

Objectives

This review aims to comprehensively discuss current amyloidosis literature to elucidate the clinical manifestations, diagnosis, as well as diagnostic challenges associated with intestinal amyloidosis.

Clinical manifestations

Diarrhea

Described in 11–46% of patients, chronic diarrhea is one of the most common symptoms of intestinal amyloidosis.[8,9,13,15] In patients with unexplained diarrhea, weight loss, malabsorption, or protein loss, amyloidosis must be considered. The clinical experience of patients is not characteristic but usually the diarrhea is prolonged (longer than 4 weeks), postprandial, and may be accompanied by fecal incontinence or malnutrition.[13,16] Some patients present with watery diarrhea, with no blood, mucus or pus. Less often, patients present with bloody diarrhea associated with fever and abdominal pain or cramping.[17–19] Recurrent diarrhea may be associated with muscle weakness, electrolyte disturbances, or peripheral paresthesia in the lower extremities.[16]

Differential diagnosis requires the exclusion of infectious and parasitic causes of diarrhea, including *Salmonella, Shigella, Campylobacter,* and toxin A for *Clostridium difficile* analysis. In digestive tract amyloidosis, fecal calprotectin may be indicative of mild intestinal inflammation.[20,21] Radiological examinations are non-specific; however, abdominal computed tomography (CT) scans may show edematous wall thickening of the small bowel and colon.[21] The results of ileocolonoscopy are non-specific, either with an accentuated vascular pattern along the colon, diffusely distributed petechial mucosal suggillations, or shallow erosions in the colon and terminal ileum.[12,16,22] In some patients,

the presence of diffuse ulcerations with necrotic and hemorrhagic materials in the colon were observed.[19] In all described cases, the deposition of amorphous hyaline material infiltrating the submucosa wall in the colon was verified using hematoxylin and eosin (H&E) staining. Additionally, Congo red staining allowed for the confirmation of amyloidosis by the detection of green birefringence on amyloid depositions in the lamina propria of the colonic mucosa.[16,18,19]

The mechanism behind the presentation of diarrhea in patients with amyloidosis is not fully understood. It is generally suggested that diarrhea arises due to motility disturbances of the gastrointestinal tract which are caused by autonomic neuropathy and intestinal inflammation.[13] Moreover, abnormal small intestinal motility facilitates the bacterial contamination of the small intestine. Bacterial contamination is a common underlying cause of diarrhea and should be routinely tested for. Further, if diarrhea is observed, treatment with antibiotics should be considered.[23] Moreover, the malabsorption of bile acid, commonly associated with abnormal motility, also contributes to worsened neuropathological symptoms.[24] The treatment of chronic diarrhea in patients with amyloidosis is non-specific and is mostly aimed at controlling the symptoms. In some cases, octreotide and steroids can be used in refractory diarrhea with protein-losing enteropathy.[25] Causal treatment for intestinal involvement is available only in some types of amyloidosis. For example, in AA amyloidosis, the treatment should be focused on the therapy of the underlying disease. For the most common type of amyloidosis, AL amyloidosis, its treatment is best accomplished through high-dose chemotherapy followed by autologous stem-cell transplantation in patients qualifying for such an intensive approach, and by conventional chemotherapy in the remainder of cases. Further, treatment must be implemented after the final confirmation of the diagnosis and should be carried out in a reference center by a multidisciplinary team consisting of a hematologist, cardiologist, nephrologist, neurologist, and gastroenterologist.

Malnutrition and unintentional weight loss

Large clinical studies assessing the manifestations of amyloidosis have reported unintentional weight loss to be the most reported symptom of this disease.[9,26,27] The nutritional disorder is prevalent among patients with intestinal amyloidosis and is undoubtedly underdiagnosed. It is hypothesized that malnutrition is associated with asthenia and lack of appetite. Typical laboratory results, including ferropenic anemia, folic acid, and vitamin B_{12} deficiency or hypoalbuminemia, have highlighted these factors as potentially significant contributors to malnutrition in amyloidosis.[28] Additionally, there is a significant correlation between malnutrition, poor quality of life, as well as a shorter survival time in patients with amyloidosis.[27]

The pathogenesis of weight loss is multifactorial. Furthermore, it may be observed in patients with amyloidosis even before the onset of any other symptoms.[13,29] Amyloid deposition probably contributes to weight loss through an increased metabolism due to enhanced inflammatory reactions and oxidative stress.[13] Moreover, in patients with intestinal amyloidosis, chronic diarrhea, malabsorption, nausea, and vomiting, or the feeling of early satiety could be contributing factors that negatively affect the patients' energy intake. In a study analyzing the clinical features of patients with AL amyloidosis, the symptoms associated with weight loss were reduced appetite (43%), altered taste of food (27%), early satiety (25%), or fatigue (21%).[27] Such data infers that amyloidosis should always be considered as a possible cause of unintentional weight loss, especially in older patients. Lobo et al.[30] reported jejunal biopsy data which showed that, in patients over 65 years of age with suspicion of intestinal malabsorption, amyloidosis was one of the most diagnosed causes of malnutrition besides the villous atrophy, intestinal lymphangiectasia, unspecific jejunitis, and Whipple's disease.[30]

In AA amyloidosis, the management of weight loss in intestinal amyloidosis is focused on establishing an accurate, final diagnosis and the subsequent treatment of the underlying disease. Dietary advice must be considered early in the course of the disease and should include small-volume meals with low soluble fiber and fat content. Patients with weight loss, nausea or vomiting due to intestinal dysmotility can be treated with nutritional support, especially with fat-soluble vitamins, and medications such as prokinetics and antiemetics. For severe malabsorption, total parenteral nutrition may be useful if dysmotility-related symptoms are disabling, and the patient becomes malnourished.[31]

Intestinal bleeding

Intestinal amyloidosis may also manifest with upper or lower gastrointestinal hemorrhage. Patients may complain of coffee-ground emesis or melena as a sign of bleeding from the duodenum. Additionally, they may present with hematochezia, indicative by the passage of bright red blood primarily from the lower digestive tract.[32,33] Intestinal bleeding occurs as a symptom in 4–36% of patients with digestive tract amyloidosis and may be caused by erosions, ulcerations or generalized oozing without a particular source.[15,33–35] The initial diagnosis is made using endoscopic examination and is confirmed with biopsy and histopathologic analysis of amyloid deposits. Endoscopic features of amyloidosis also include punctate, erythematous lesions that appeared scalloped, ulcerated and hemorrhaged on contact.[12,36]

Several mechanisms have been reported by which amyloidosis can induce intestinal hemorrhage. One of the possible explanations is the association between AL amyloidosis and coagulation abnormalities, which can increase the risk of intestinal hemorrhage. Mumford et al. examined 337 patients with AL amyloidosis.[34] Their data indicated that the most common coagulation abnormalities were

prolongation of the thrombin time associated with hepatic amyloid infiltration, proteinuria and hypoalbuminemia, and followed by a prolongation of the prothrombin time.[34] Other well-defined mechanisms for amyloidosis hemorrhage involve localized intestinal ischemia, which occurs when all layers of the intestine and blood vessel walls are infiltrated. This may lead to diffuse mucosal oozing with necrosis and amyloid deposition in the vessel walls. Together, these factors induce fragility and subsequent hemorrhage.[36]

The diagnosis of amyloidosis is important after the initial bleeding has been controlled, as there are treatment options available that can have a significant impact on the disease course. The intestinal hemorrhage may stop spontaneously without intervention; however, the bleeding caused by amyloidosis tends to relapse and endoscopic or surgical procedures may be needed.[33,36]

Intestinal dysmotility and pseudo-obstruction

When the patient has no predisposing factors, physicians may not suspect intestinal amyloidosis as a cause of dysmotility and the pseudo-obstruction of the small or large intestine.[35,37] The delayed transit time in intestinal amyloidosis is similar to that seen in other systemic diseases, e.g., scleroderma. Patients usually present with chronic obstructive symptoms such as constipation and acute phases of pseudo-obstruction. Further, their symptoms may include severe colicky pain, an inability to pass feces and flatus, and progressive abdominal distension. In patients with intestinal amyloidosis, plain abdominal radiographs have shown a markedly diffuse dilatation of the small or large intestine with different air-fluid levels.[38] Clinical manifestations and radiological findings are very suggestive of acute mechanical obstruction that mimics the indication for surgical intervention. The final confirmation of amyloidosis may be achieved through the biopsy of the colon. It is reported that deposits of pink amorphous material stained with Congo red and displayed the typical apple-green birefringence are indicative of intestinal amyloidosis. Moreover, the recognition of intestinal amyloidosis in patients with unexplained etiologies of luminal obstruction is important to avoid laparotomy, which would be of no benefit.[39]

The reasons for intestinal dysmotility in amyloidosis patients are not fully understood. However, the malfunction of the autonomic and enteric nervous systems, including the depletion of intestinal neuroendocrine cells, seems to be of importance. The underlying mechanisms are myopathic and induce neuromuscular dysfunctions due to the deposition of amyloid within the smooth muscle of the intestine or infiltration of amyloid into the myenteric plexus which causes pressure-induced atrophy of the adjacent fibers.[37] The intestinal dysmotility in amyloidosis patients is likely a sequential process that

starts with the deposition of amyloid in the vasculature, followed by the involvement of the muscular layers, and potentially affects the myenteric plexus. This final stage is accompanied by clinical symptoms of severe intestinal dysmotility.[40]

Perforation

Perforation is a very rare complication of intestinal amyloidosis; however, it may be the first sign of this disease and usually requires surgical intervention.[41,42] In such cases, patients suddenly develop severe pain with abdominal wall tenderness and peritoneal signs. An abdominal radiograph or CT may reveal extraluminal free air and stool around the perforated colon. An emergency exploratory laparotomy should be performed based on the preoperative diagnoses of intestine perforation and acute generalized peritonitis. In 1 patient, a perforation 4 cm in diameter that was accompanied by a surrounding hematoma and necrotic tissue at the mesenteric site of the sigmoid colon was visible.[43] In another patient, a section of the sigmoid colon having 26 cm in length and showing focal mucosal ulceration with perforation, and the surrounding serosal reaction was removed.[44] In all cases, histological examination revealed vascular wall thickening which stained positive with the Congo red stain, and vascular lumen stenosis with ischemic changes in the small intestine.[43,44]

The mechanism behind intestinal perforation is based on massive amyloid deposits which seem to induce vascular lumen stenosis and result in intestinal ischemic changes. In most cases, the submucosal blood vessels are the earliest and most frequent site of amyloid deposition. Amyloid fibrils gradually accumulate in both the vessels and intestinal wall, causing mucosal impairment as well as ischemic changes due to vascular involvement.[45] This can lead to blood vessel occlusion with resulting infarction or perforation.[43,44]

Amyloidomas

Tumor-like lesions (amyloidomas) are detected in 3.5% of patients with amyloidosis, not only in the digestive tract but also in the lungs, urinary bladder, prostate, epipharynx, and anterior mediastinum.[3] From a gastroenterological point of view, there may be single or multiple lesions, localized in all parts of the digestive tract; however, these lesions are observed most often in the small bowel and colon. Amyloidomas of the small bowel, without extraintestinal manifestations, are rare and are typically diagnosed after resection because of potential complications including stricture and hemorrhage, or the difficulty in discriminating malignant lesions.

Patients with colon amyloidomas complain of constipation, progressive abdominal distention and discomfort with dilatation of colonic segments shown in the abdominal X-ray. Some patients manifest recurrent bleeding

and the amyloid deposition in the vascular walls in areas adjacent to the tumor is visible under pathologic examination.[3,46]

Amyloidomas are characterized in colonoscopy as circumferential tumor-like lesions, which resemble colon cancer.[47] In all cases, a differential diagnosis with intestinal lymphoma, adenocarcinoma and gastrointestinal stromal tumors should be carefully assessed.[28] Multiple biopsies, not only from obviously abnormal lesions but also from normal-appearing intestinal mucosa, are recommended for the definitive confirmation of the diagnosis. In addition, the results of analysis of dysplastic gland proliferation and neoplastic infiltration in amyloidomas should be negative. Surgical treatment is often prescribed for undiagnosed amyloidomas; however, conservative strategies can also facilitate an improvement in tumor treatment. For example, in the clinical case reported by Ando et al., the tumor was completely diminished after one month of observed bowel rest.[47]

Although the mechanism underlying the development of such tumor-like lesions is unclear, the involvement of the amyloid deposits in the vascular wall appears to lead to ischemic changes which induce nodular elevations that resemble colon neoplasms. The extensive amyloid deposits affect the entire wall thickness, destroy the mucosa, and allow for the deep infiltration of amyloid into the muscularis propria, which induces luminal narrowing of the blood vessels.[48,49]

Diagnosis of intestinal amyloidosis

Without a known history of amyloidosis, the clinical diagnosis of intestinal involvement is very difficult. Endoscopic findings of intestinal amyloidosis are not specific and are characterized by fine granular appearance, erosions, ulcerations, mucosal friability, or multiple protrusions. Further, the type of symptoms does not predict endoscopic findings; however, the histopathological results partially correlate to the different types of amyloid fibril protein. The gold standard for diagnosing amyloidosis is a tissue biopsy of an affected organ which is then stained with Congo red stain. A positive sample demonstrates a green birefringence under polarized light. In patients with AA amyloidosis, amyloid deposits mainly in the lamina propria mucosae and perivascular walls in the submucosa of the gastrointestinal tract. Therefore, tissue with a fine granular appearance and mucosal friability may be observed endoscopically in some patients with AA amyloidosis. Conversely, in patients with AL amyloidosis, amyloid tends to massively deposit in the muscularis mucosa, submucosa and muscularis propria. Endoscopically, multiple polypoid protrusions and thickening of the folds are slightly more characteristic of AL amyloidosis.[12,50]

As systemic amyloidosis often affects the gastrointestinal tract from the early phase of illness, even without clinical symptoms, the digestive tract is the preferential site for biopsy with regard to procedural safety and sensitivity. Examinations of biopsies from the upper gastrointestinal tract revealed higher positive rates of a biopsy of the stomach and duodenum (91.3%) relative to those taken from the stomach only (62.1%). Additionally, the high sensitivity of the duodenum biopsies was consistent with the findings that the small intestine is mostly occupied during amyloidosis.[8] However, apart from the duodenum and distal part of the ileum, the small intestine is relatively difficult to access with endoscopic examinations. In some patients, push enteroscopy or capsule endoscopy are helpful to detect lesions that are limited to the jejunum. Endoscopic ultrasonography of these lesions may reveal the hypoechoic thickening of the mucous and the submucosal layers.[51] Barium enema or CT findings are non-specific and are characterized by regular thickening of the folds, jejunalization of the ileum and granular mucosal pattern In the case of colonic involvement, luminal narrowing and the loss of colonic haustrations are also characteristic of observations made using CT.[52]

The diagnosis of amyloidosis is based on histopathological findings; however, neither endoscopic imaging nor the Congo red staining is sufficient to distinguish the amyloidosis subtype. Amyloid typing is essential to make a correct diagnosis and initiate the appropriate treatment. Currently, the best methods to discern the amyloid type are immunohistochemistry, immunoelectron microscopy or mass spectrometry (the highest specificity and sensitivity, but available in very few health centers worldwide).[5,53] It is worth emphasizing that there are no specific biomarkers to diagnose or predict amyloidosis; however, N-terminal pro-brain natriuretic peptide (NT-proBNP) is increased during the early stages of cardiac involvement. Additionally, proteinuria may be the first symptom of renal amyloidosis.[5] In all patients, serum-free light chain (FLC) and serum and urine immunofixation electrophoresis should be performed. In any case of amyloidosis, the infiltration of other organs, especially the heart and kidneys, should be assessed using both laboratory and imaging methods. The prudent use of invasive tests is recommended and peripheral tissue biopsy with abdominal fat aspirate is preferred. The biopsy of involved organs, such as the kidneys or liver, is characterized by high sensitivity but also by a risk of complications, and should be performed only when other methods fail to confirm the diagnosis of amyloidosis.[2,5]

Diagnostic challenge

Intestinal amyloidosis can easily be misdiagnosed and confused with several other diseases of the digestive tract, especially with IBD. Jean et al. reported a clinical case of a family with hereditary lysozyme amyloidosis who had clinical manifestations limited to the gastrointestinal tract.[54] Three members of the family had the initial

diagnosis of IBD with a history of abdominal pain, diarrhea and rectal hemorrhage. Further, pancolitis was also observed using colonoscopy. Finally, in addition to inflammatory lesions, amyloid deposits were detected in rectocolic biopsies as well as biopsies taken from the stomach and duodenum. One patient presented with ileal ulcers, as confirmed with lower endoscopy, which suggested the diagnosis of IBD; however, colon biopsies revealed amyloid deposits without inflammatory infiltration.[54] Additionally, the same patients had non-specific IBD symptoms and partially responded to standard treatment of inflammatory colitis. In other reported cases, amyloidosis was only considered when a patient with an initial diagnosis of IBD presented with heart failure and restrictive cardiomyopathy.[55] Some patients may also have symptoms of systemic amyloidosis, such as macroglossia or proteinuria, which are characteristic of kidney involvement. These observations can lead to the final diagnosis of amyloidosis.[8,15] However, it is much more difficult to recognize the disease with the isolated involvement of 1 organ. Together, these data indicate that a high degree of clinical suspicion is needed to make an early diagnosis of amyloidosis in patients with non-specific symptoms.

The prevalence of secondary amyloidosis among IBD patients is 0.53–2.0%; however, epidemiological data suggest that secondary amyloidosis may be under-diagnosed. IBD patients with AA amyloidosis are significantly associated with proteinuria and cardiac comorbidities, including cardiomyopathy, heart failure, or atrial fibrillation.[56,57] Therefore, these patients should be routinely screened for kidney and heart diseases. Physicians and gastroenterologists involved in the treatment of IBD patients should be aware of these complications and be vigilant in identifying the early signs and symptoms of amyloidosis. The phenotype most frequently associated with amyloidosis is males with aggressive and extensive Crohn's disease (CD), fistulizing behavior and perianal disease; or with the development of proteinuria and renal failure.[58] The incidence of amyloidosis is significantly higher in patients with small and large bowel involvement and with a long duration of the disease with a cumulative incidence of 1.0% at 10 years and 5.7% at 20 years after CD onset.[57]

It is known that the clinical and endoscopic imaging of amyloidosis may be very similar to other intestinal diseases and that a final diagnosis is possible only after pathologic examination. Recently, a 61-year-old patient with Behçet disease (BD) and massive hematochezia was described.[58] In that case, the colonoscopy showed multiple, small, round-shaped ulcers extending from the ascending to the transverse colon. A biopsy revealed amorphous eosinophilic extracellular deposits in the vascular wall. The deposits stained positive on Congo red staining and showed apple-green birefringence under polarized light. Moreover, immunohistochemistry revealed that the deposits were positive for the lambda light chain. These lines of evidence led to an additional diagnosis

of AL amyloidosis. In this case, the endoscopic images differed from those typically observed in BD in which multi-segmented and diffuse colonic involvement is rare as the images portrayed a visual combination of the endoscopic features of BD disease and intestinal AL amyloidosis.[58,59]

Conclusions

In conclusion, since the clinical presentation of intestinal amyloidosis is frequently non-specific, establishing an accurate diagnosis requires careful endoscopic, radiologic and histopathological evaluation. Gastroenterologists must become confident with imaging findings of intestinal amyloidosis to make a correct differential diagnosis. These competencies will facilitate both proper diagnostic and therapeutic management. Intestinal amyloidosis may present with more varieties of clinical symptoms than previously thought. The final diagnosis requires a confirmation based on biopsy with histopathological confirmation and subtype assessment. The use of endoscopy with pathological examinations should be actively considered as early as possible, as the several types of amyloidosis are currently treatable, and the best results can be achieved in the initial phase of the disease. To conclude, amyloidosis is a rare, complex disease, and its proper diagnosis requires the cooperation of physicians of many different disciplines.

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