Weight loss, diarrhea, and polyneuropathy: could it be amyloidosis?

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ABSTRACT

Background: Amyloidosis is a multisystemic disease that may be hereditary, characterized by the deposit of amyloid in the extracellular space. Transthyretin-mediated (ATTRm) amyloidosis is the most common subtype of heredofamilial amyloidosis. The diagnosis is based on clinical suspicion and amyloid in tissues. Hepatic transplantation is the only treatment that prevents the synthesis of the amyloidogenic variants of transthyretin protein.

Case Presentation: A 34-year-old male presented with weight loss, gastrointestinal symptomatology, and polyneuropathy associated with histopathologic deposits of amyloid in gastrointestinal and fat tissue as well as peripheral nerve.

Conclusion: Hereditary familial amyloidosis (HFA) is a relatively rare disorder that leads to erroneous and delayed definitive diagnosis. Therefore, the diagnosis should be first based on a suspicion of the disease, and then proceed according to complete protocol.

Keywords: Amyloidosis, familial amyloidosis, polyneurophaty, diagnosis, biopsy.

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Background

Amyloidosis is a range of diseases characterized by abnormal fibrous, intra and extracellular, proteinaceous deposits in organs and tissues termed amyloid. So far, 30 proteins and peptides have been identified as the main components of the amyloid [1,2]. Despite the obvious differences in primary sequences and structure, these amyloidogenic molecules all appear to share a common β-sheet conformation of their polypeptide that self-assemble perpendicular to the axis of the fibril. It is likely that this characteristic confers the fibrillar, proteolytic resistant, and insoluble characteristics to all forms of amyloid [3]. The relevance of amyloid depends on its extracellular accumulation grade, ranging from local microscopic deposits of no clinical significance to extensive, lethal infiltration of vital organs. Rudolph Virchow adopted the term “amyloid” in 1854, first introduced by Schleiden in 1838 to describe the vegetable starch, referring to the deposits of tissue material that stains in a similar way to cellulose when it is exposed to iodine [4]. There are several subtypes of amyloidosis, local and generalized forms, all with different amyloid precursors: AL (for Amyloid/Light chain) also called primary or myeloma-related, Amyloid A (AA) (for AA, so called because this serum AA was the first to be chemically characterized) also named secondary or reactive amyloidosis due to chronic inflammatory or neoplastic processes, and ATTR (for Amyloid/ transthyretin protein TTR, the acronymous of transthyretin an abnormal protein by a single amino acid) or familial amyloidosis (FA). TTR is a tetrameric plasmatic protein synthesized mainly in the liver and to a lesser extent in the choroid plexus and retina, responsible for transporting thyroxin and the protein linked to retinol. The estimated world prevalence of amyloidosis is 50,000 individuals with variable phenotypic presentations of the disease. Seventy-five percent present the primary form, 5% the secondary form and less than 5% develop an FA [1,4]. The hereditary pattern of the FA is the autosomal dominant, with its most prevalent type being mediated by transthyretin (ATTRm). Other recognized types include Aapo AI (Amyloid/Apolipoprotein AI), Aopo AII (Amyloid/ Apolipoprotein AII), and gelsolin (Agel) amyloidosis [5]. The latest systemic type of amyloidosis has been described and called leukocyte cell-derived chemotaxin 2 amyloidosis, which is highly prevalent in the Hispanic population, with a strong ethnic bias, affecting mainly Mexican people, Punjabis, people from the First Nations in British Columbia and native Americans [6]. The clinical picture of amyloidosis is heterogenous and nonspecific, determined by the affected organ or system. The diagnosis is based on clinical suspicion and the

demonstration of the amyloid substance in tissues. A correct differential diagnosis is important since the management and prognosis may be completely different according to the source [7]. Additional tests such as immunohistochemistry, immunofluorescence, genetic tests and electron microscopy of amyloid deposits, assist in the or it helps in the identification of amyloidogenic protein, so that, familial forms of amyloidosis can be ruled out [8,9]. At present, Hepatic Trasplantation (HT) is the only treatment for the prevention of synthesis of amyloidogenic variants of TTR [10]. Here, we present a case of FA associated with cardiac, gastrointestinal, and neurologic affections.

Case Presentation

A 34-year-old male, without chronic illnesses, but with cocaine consumption for 6 weeks before hospital admission. Four years before admission he started with a dry cough associated with dyspnea and cyanosis. Thereafter,

Table 1. *Laboratory and immunologic studies.*

LABORATORY TEST	PARAMETER	RESULT	REFERENCE VALUE
Blood chemistry	Glucose	81 mg/dl	70-100 mg/dl
	Creatinine	0.92 mg/dl	0.7-1.3 mg/dl
	AST	26 UI	0-35U/l
	ALT	47 UI	0-35 U/l
	AF	64	36-150 U/l
	LDH	127	60-160 U/l
	Total bilirubin	0.57 mg/dl	0.3-1.2 mg/dl
	Albumin	3.4 g/l	3.5-5.4 g/dl
Cell blood count	Hemoglobin	12 g/dl	14-18 g/dl
Urianalysis	pH	5.0	4.6-8.0
	Urine density	1.025	1.003-1.030
	Erythrocytes	10-15 × field	0-2 × field
	Bacteria	Abundant	Negative
	Leukocytes	20-30	0-10 × field
24 hours urine	Creatinine clearance	164.49 ml/minute	70-150 ml/minute
	Proteins	0.30 g/24 hour	0.01-0.30 g/24hour
Bence jones protein		Negative	Negative
Beta 2 microglobulin		3.0 ug/ml	<2.0 ug/ml
Viral panel	VIH/VHB/VHC	Negative	Negative
Torch	Toxoplasma/Rubeola/CMV/VHS	Negative	Negative
Toxinas A B		Negative	Negative
Coprologic	pH	6.5	5.8-6.4
	Sugars	Negative	Negative
	Blood	Positive	Negative
	Food without digestion	Negative	Negative
	Fat in feces	2.6 g/24 hour	5 gr/24 hour
	Macroscopic parasites	Negative	Negative
Coproparasitoscopic		*E. coli* cysts	Negative
Fresh ameba		Negative	Negative
Stool culture		Normal enteric flora	Normal enteric flora
Inmunoglobulins	IgG	1,040 mg/dl	700-1,800 mg/dl
	IgA	128mg/dl	100-480mg/dl
	IgM	166 mg/dl	60-250 mg/dl
Anti DNA		1:80	Negative or until dilution 1:80
Complement	C3	64 mg/dl	80-200 mg/dl
	C4	19 mg/dl	10-50 mg/dl
Anti gliadin, anti endomysium, febrile reactions, PPD.		Negative	Negative

he presented nausea, postprandial vomiting, regurgitation, dyspepsia, and steatorrhea treated with loperamide (20-30mg). Eight months before admission he presented weight loss of 18 kg, erectile dysfunction, urinary incontinence, and paretic gait. Multiple laboratory tests (Table 1), along with endoscopies, histopathologic analysis, echocardiogram, and electromyography were performed but reported as normal (Table 2). Notably, all gastrointestinal and sural nerve biopsies analyzed were reported as normal. Consequently, a conclusive diagnosis was not reached. His mother has a history of chronic renal insufficiency probably secondary to amyloidosis. At the time of admission to our hospital, the physical examination of the patient revealed bilateral symmetric mydriasis with absent light and consensual reflexes, considerable muscular wasting, muscle weakness in all four extremities, absence of deep tendon reflexes in lower extremities, and bilateral symmetric hypoesthesia in a stocking distribution. Because of chronic diarrhea a small bowel series was performed, which reported accelerated intestinal transit (2 hours), and normal intestinal mucosa. Because of the mydriasis, a magnetic resonance imaging of the brain was performed, which showed hyperdense lesions in the frontal subcortical white matter with cortico-subcortical atrophy. An abdominal ultrasound revealed diffuse parenchymatous damage in

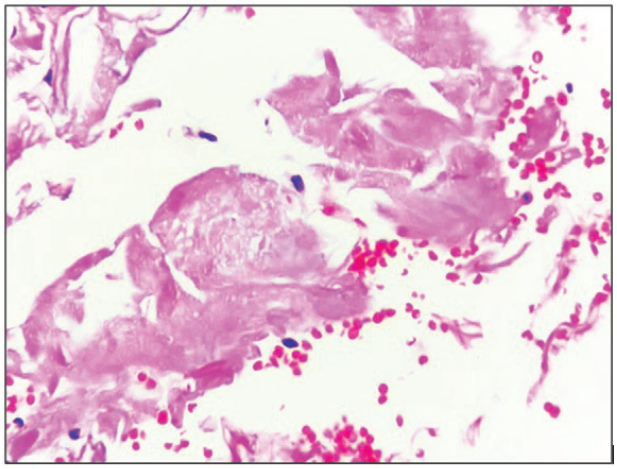

Figure 1. *An acellular and irregular intense eosinophilic deposit was observed interstitially in the periumbilical adipose tissue biopsy, probably corresponding to amyloid. H&E stain 200×.*

Table 2. *Ancillary test.*

Echocardiogram	Nonobstructive symmetric hypertrophic cardiomyopathy, probable amyloid infiltration, EFLV 80%, mild mitral insufficiency, mild tricuspid insufficiency without pulmonary hypertension.
Electromyography	Sensorimotor polyneuropathy of axonal and demyelinating type, more severe in lower extremities.
Colonoscopy	Normal terminal ileum and colon. Biopsies taken from both organs.
Endoscopy	Moderate erosive gastritis with *H. pylory*. Sliding hiatal hernia.
Biopsies of ileum and colon	Amyloidosis in submucosa
Biopsies of periumbilical fat	Amorphous material compatible with amyloidosis.

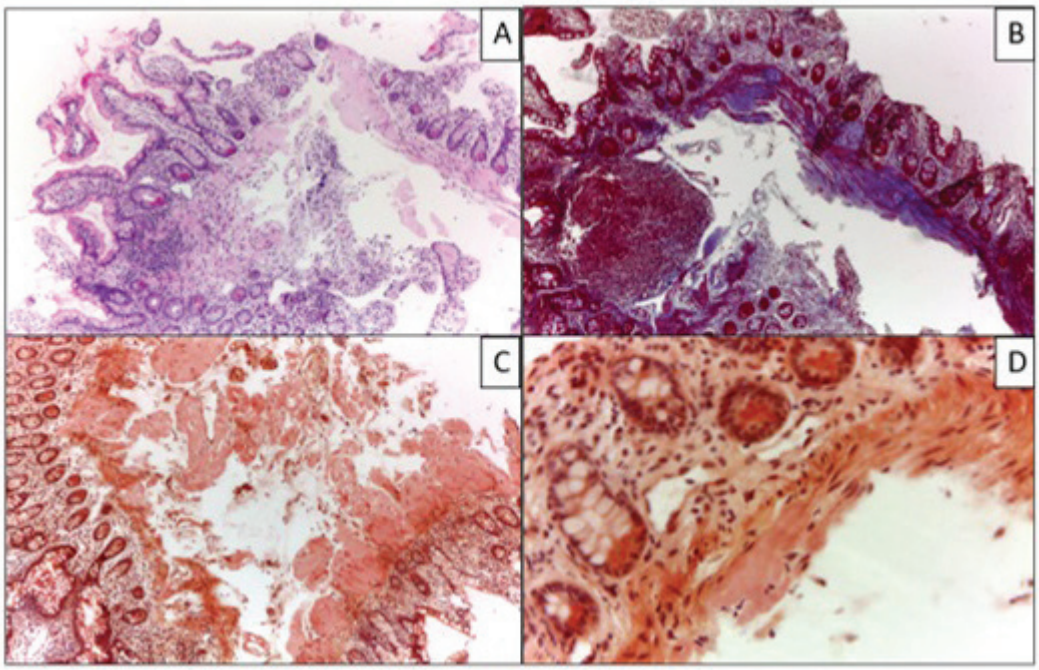

Figure 2. *Photomicrographs of ileum biopsies. Note the presence of a deposit of eosinophilic material at lamina propria, muscularis mucosae, and submucosa layer (A), as well as their blue and red mixed stain with the trichromic method (B), and the congophilic stain of these ileum layer (C-D). A: H&E, B: Trichromic Masson method, C-D: Rojo Congo stain. A-C 100×, D 400×, total magnifications.*

the liver and chronic damage to the kidneys. An echocardiogram revealed non-obstructive symmetric hypertrophic myocardiopathy versus probable infiltration, with a left ventricular ejection fraction (LVEF) of 80%. Hence, given the presence of hypertrophic cardiomyopathy, disturbance of intestinal motility and autonomic and peripheral neuropathy, the possibility of a disease secondary to amyloid deposit was suspected. Therefore, biopsies from mucous membranes of the ileum and colon periumbilical fat, and sural nerve were obtained and processed to paraffin sections, stained with H&E,trichromic Masson method, and Congo red. The last staining was analyzed with a polarized light microscope. A kidney biopsy from a pediatric case of amyloidosis was used as a positive control of the Congo red stain. The histopathological findings revealed the presence of anacellular and irregular intense eosinophilic deposit observed interstitially in the periumbilical adipose tissue biopsy, probably corresponding to amyloid (Figure 1). In ileum biopsies, a similar eosinophilic deposit was observed at lamina propria, muscularis mucosae, and submucosa layer (Figure 2A), which exhibited a mixed blue and red staining with the trichromic method (Figure 2B). These eosinophilic and blue-red stained layers of ileum positive for Congo red staining (Figure 3C-D). In the sural nerve biopsy, a typical green-apple birefringence was found in cross-polarized light in Congo red-stained sections, located at endoneurium and in the arteriolar wall (Figure 3). The selectivity of this gold standard technique was confirmed in the positive control kidney histological sections (Figure 4).Therefore, a diagnosis of hereditary FA was presumed, but its precise confirmation has not yet been achieved, due to the abandonment of its study protocol.

Discussion

Hereditary amyloidosis mediated by transthyretin (ATTRm) is a multisystemic disease conditioning diverse clinical manifestation (Table 3), which is transmitted in an autosomic dominant form with variable penetration. It is considered a rare disease, with a prevalence of less than 1 per 100,000 inhabitants. Presently, over 120 mutations are known to cause it. Mutation VAL30MET is the most frequent worldwide, being endemic in Portugal, Japan, and Sweden. Predominantly affects the neurologic system in 15% of patients, with an ascending sensori-motor, symmetric polyneuropathy which initiates in the lower extremities [11]. Cranial nerves are intact, except for those involved in pupillary reflexes, exhibiting festooned pupil, vitreous opacity, and glaucoma [2]. It may be linked to dysautonomia, presenting as orthostatic hypotension, erectile dysfunction, urinary incontinence, and gastrointestinal symptoms, with the latter arising either from direct involvement of the gastrointestinal system or amyloid infiltration of the autonomic nervous system, observed in up to 98% of cases [1]. It usually begins at the end of the second or third decade of life and up to 43% of the carriers present cardiac affection (conduction disturbances, atrial fibrillation, restrictive myocardiopathy and more often cardiac insufficiency) which is a frequent cause of mortality [12]. Other more unusual clinical manifestations are decreased peristalsis and dysphagia [6,13]. A confirmed diagnosis is based on a biopsy of the tissue or organ infiltrated where the typical birefringence of apple green color, stained by Congo red under polarized light fluoroscope is expected to be demonstrated.

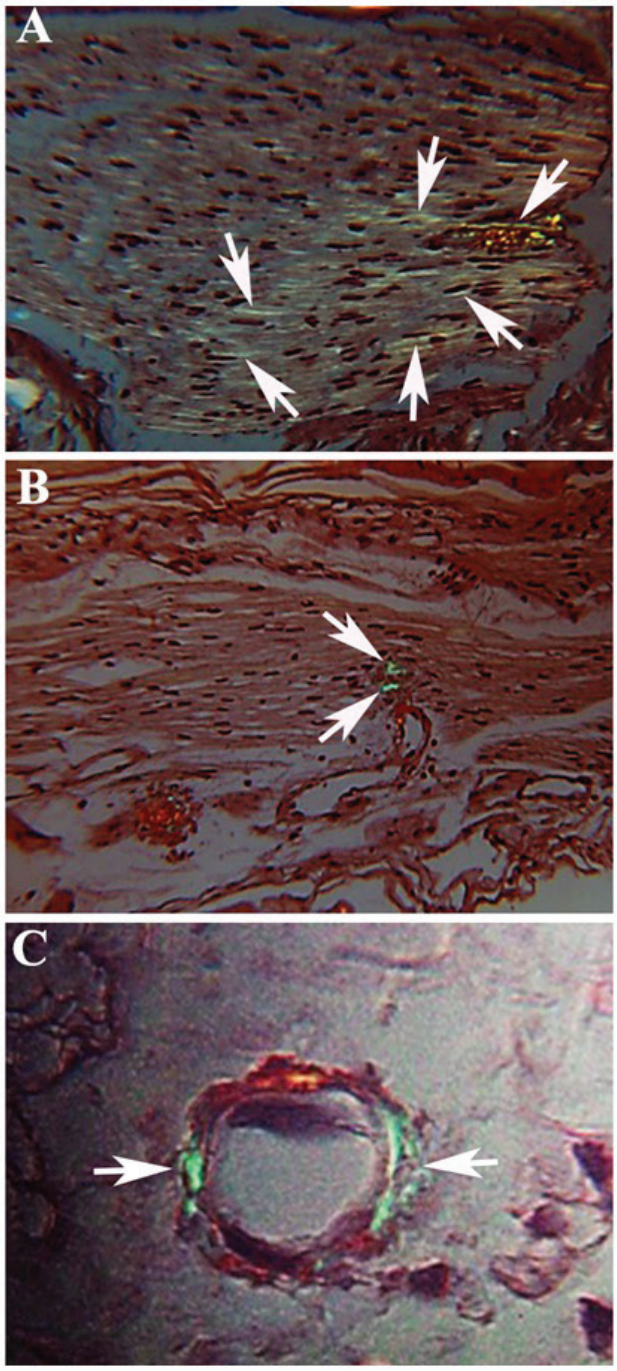

Figure 3. *Photomicrographs of longitudinal nerve sections stained with Congo red. The characteristic apple- green birefringence of amyloid deposits was located at endoneurium (A, white arrows), and wall of small blood vessels (B, white arrows)- Note the red apple green birefringence, and dichroism coloration at arteriole wall (C, white arrows). Polarized light microscope. Congo red stain. A, B 200×; C, 1250×*

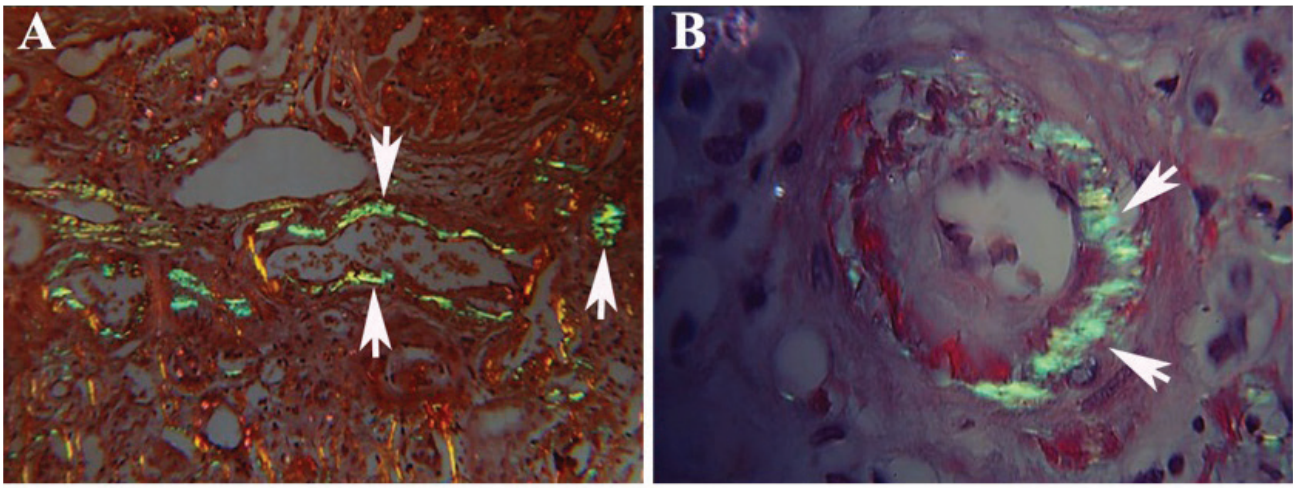

Figure 4. *Photomicrographs of kidney biopsy from a pediatric case of amyloidosis. This specimen was used as positive control of the Congo red stain. White arrows point out the presence of amyloid deposits in the wall of intrarrenal blood vessels based on apple-green birefringence and dichroism characteristic of the molecular periodicity of amyloid. Polarized light microscope. Congo red stain. A,200×; B, 1,250×*

Table 3. *Main clinical manifestations of FA.*

CLINICAL MANIFESTATIONS OF FA		
AFFECTED ORGAN	**MANIFESTATIONS**	
Cardiac	Hypertrophic of left ventricle (13%)	Radio discordant voltage/mass
	Hypertrophic hypertensive	Radio discordant voltage/mass Intolerance to beta blockers
	CHF with preserved EFLV (10%)	Not dilated hypertrophy of left ventricle
	Not complicated degenerative aortic stenosis (30%)	Slow flow Low paradoxical gradient Thinning of atrioventricular valves
Neurologic	Chronic inflammatory demyelinating polyneuropathy (15%)	Neuropatic pain Symmetric neuropathy of upper extremities
	Idiopathic axonal polyneuropathy	Dysautonomia Erectile dysfuntion
	Carpal tunnel syndrome (33-49%)	Neuropatic pain
	Autonomic neuropathy (10%)	Orthostatic hypotension Recurrent urinary infections Urine retention Erectile dysfunction Sweating disturbances
	Motor neuropathy (18%)	Decrease in amplitude of movements
	CNS (approx. 5%)	Progressive dementia Headache Ataxia Epilepsy Spastic parylisis Stroke-like episodes
Gastrointestinal	Irritable colon syndrome	Chronic diarrhea
	Pseudo- obstruction	Nausea and vomiting
	Early satiety	Constipation
	Involuntary weight loss	
Ocular	Vitreum opacity	Glaucoma
	Disturbances of conjunctival vessels	Papillary abnormalities
Renal	Proteinuria	Renal failure
		Nephrotic syndrome

Gertz et al. BMC Family Practice; Am J Manag Care. 2017;23:S107-S112.

CHF: Congestive heart failure, EFLV: ejection fraction left ventricular, CNS: Central Neuronal System.

Table 4. *Drugs for treatment of ATTR.*

SUPPRESSION OF TTR SYNTHESIS	STABILIZATION OF TTR [B]	DISPOSAL OF DEPOSITS[F]
HP Genetic mufflers: siARN (ALN-TTR)*, OAS (ISIS-TTR_{RX}). [a]	Tafamidis[c] Diflunisal[d] Tolcapone[e]	Doxycycline Doxycycline-TUDCA EGCG (green tea) PRX004 Anti-SAP+CPHPC

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AntiSAP + CPHPC: antibody against serum component P amyloid + (R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid; EGCG: epigallocatechin-3 galato; OAS: antisense oligonucleotides; siARN: interference ARN, TTR: transthyretin; TUDCA: tauroursodeoxycholic acid.

*siARN (ONPATTRO®): Approved by EMA for the treatment of AhTTR with polyneuropathy in stages 1 or 2.

[a, f] Molecules under investigation for the treatment of patients with ATTR cardiac amyloidosis and AL.

[b] Have demonstrated so far, their efficacy in ATTRm polyneuropathy.

[C] Orfan drug approved by EMA to delay neurologic progression. The study ATTR-ACT, showed a decrease in mortality by 30% and in rate of hospitalization by 32%.

[d] Non-esteroidal antiinflammatory that has demonstrated to stabilize the molecule of TTR *in vitro*.

[e] Oral inhibitor of catechol-O-methyltransferase, which has a capacity to bind with TTR *in vitro* of patients with ATTRwt and Val122Ile.

In case this is not possible, the recommendation is aspiration biopsy of abdominal subcutaneous fat (diagnostic yield of 70%-80%). Medullary biopsy stained for amyloid is positive in 50% of the cases, and when combined with aspiration of subcutaneous fat, the yield may reach 80%-90%. The percentage of positivity for biopsy of rectal submucosa, kidney, liver, sural nerve, and heart is 75%, 94%, 97%, and 100%, respectively [12,14]. Until recently, the diagnosis of ATTR was essentially histologic. However, to facilitate the diagnosis, a multicentric international article was published in 2016, which put forth a new algorithm for the noninvasive diagnosis of ATTR, where the presence of classic signs of cardiac amyloidosis by image techniques, 2-3 degrees of uptake in gammagram Tc-DPD/PYP, along with the exclusion of a monoclonal protein, provides sensitivity and a positive predictive value of 100% for the diagnosis of ATTR [15,16]. The differential diagnosis should include diabetic neuropathy, chronic inflammatory demyelinating polyneuropathy, light chain (AL), amyloidosis by gelsoline, and apolipoprotein A1 [11]. The differentiation of the type of amyloidosis is carried out by immunohistochemistry using specific antibodies against the varied types of amyloid proteins: anti-AA, anti-light chains, anti-prealbumin, and anti-beta-2-microglobulin. In cases of hereditary FA, typing of transthyretin amyloid should be done [17]. To date, there is no approved specific therapy and hepatic transplantation (HT) is the only treatment for the prevention of the synthesis of amyloidogenic variants of TTR. The most accepted indications for HT are young patients, with VAL30MET mutation and being at the initial stage of the disease. Limitations for the procedure are: donor shortage, need for chronic immunosuppression, and advanced age at the time of presentation [4,10]. Post-transplant survival rate surpasses 50% at 20 years for patients with VAL30MET mutation and predominant neurologic manifestations. In contrast, patients with cardiac, leptomeningeal, and ocular amyloidosis may exhibit disease progression despite undergoing transplantation [15,16]. Nowadays, there are drugs that work at different points in the cascade of amyloidogenesis for TTR (Table 4), whose targets are suppression of synthesis, stabilization of TTR, and elimination of deposits. Several drugs are still in the last stages of experimentation for the specific treatment of this entity [15,16]. The disease has an inexorable progressive course, leading to death 7-15 years after onset of clinical manifestations. If there is cardiac affection, the median survival is approximately 75 months after diagnosis [12,16].

Conclusion

The diagnostic protocol concluded that this was a case of hereditary FAwith cardiac affection, disturbance of intestinal motility, and autonomic and peripheralneuropathy. In this case, the patient had had studies done elsewhere before admission. Frequently, ATTR is an entity with substantial diagnostic mistakes or significant delay suntil the correct diagnosis is established. In our case, the reasons were diverse, varying from the heterogeneity of its presentation to the nihilistic consideration that limita presumptive diagnosis based on heuristics. Accordingly, since the onset of this disease is insidious and the clinical manifestations may vary widely depending on the organs or tissues affected, it is of paramount importance to emphasize that the diagnosis should be first basedon a suspicion that the disease may be present, and then go on with the consequent protocol.

What is new?

Although hereditary amyloidosis with gastrointestinal manifestations and polyneuropathy is widely described in the literature, few documented information regarding its association has been publicated in Mexican and Latin American population.

Table summary

The alterations in laboratories were positive urinalysis for erythrocytes 10 to 15 per field, creatinine clearance 164.49 ml/minute, beta 2 microglobulin 3, Eliminate “tool test with positive blood, coproparasitoscopic positive for E. coli cysts”, Anti DNA 1:80, complement C3 64.

Echocardiogram with Nonobstructive symmetric hypertrophic cardiomyopathy probable amyloid infiltration, EFLV 80%, mild mitral insufficiency, mild tricuspid insufficiency. Electromyography with sensorimotor polyneuropathy of axonal and desmyelinating type, more severe in the lower extremities. Biopsies of ileum and colon with Amyloidosis in submucosa Biopsies of periumbilical fat with Amorphous material compatible with amyloidosis.

In all patients with chronic diarrhea, weight loss and neuropathy, a directed search for intestinal biopsy should be performed.

List of Abbreviations

AA	Amyloid A
AL	Light chains
ATTRm	Transthyretin mediated hereditary amyloidosis
EFLV	Ejection fraction left ventricular
FA	Familial amyloidosis
Gammagram Tc-DPD/PYP	Gammagram with 3,3-diphosphono-1,2-propanodicarboxilic/pyrophosphate tagged by technetium
HP	Hepatic transplantation
TTR	Transthyretin protein

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this case report.

Funding

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Consent for publication

Not required.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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References

1. Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. Am J Manag Care. 2017 Jun;23(7 Suppl):S107–12.
2. Shin SC, Robinson-Papp J. Amyloid neuropathies. Mt Sinai J Med. 2012;79(6):733–48. https://doi.org/10.1002/msj.21352
3. Eanes ED, Glenner GG. X-ray diffraction studies on amyloid filaments. J Histochem Cytochem. 1968;16:673–7. https://doi.org/10.1177/16.11.673
4. Sunde M, Serpell L, Bartlam M, Fraser PE, Pepys MB, Blake CC. Common core structure of amyloid fibrils by synchrotron X-ray diffraction. J Mol Biol. 1997;273:729–39. https://doi.org/10.1006/jmbi.1997.1348
5. Kyle RA. Amyloidosis: a convoluted story. Br J Haematol. 2001 Sep;114(3):529–38. https://doi.org/10.1046/j.1365-2141.2001.02999.x
6. Gertz MA, Dispenzieri A. Systemic amyloidosis recognition, prognosis, and therapy: a systematic review. JAMA. 2020 Jul;324(1):79–89. https://doi.org/10.1001/jama.2020.5493
7. Nasr SH, Dogan A, Larsen CP. Leukocyte cell-derived chemotaxin 2-associated amyloidosis: a recently recognized disease with distinct clinicopathologic characteristics. Clin J Am Soc Nephrol. 2015 Nov;10(11):2084–93. https://doi.org/10.2215/CJN.12551214
8. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet. 2016 Jun;387(10038):2641–54. https://doi.org/10.1016/S0140-6736(15)01274-X
9. Chyra Kufova Z, Sevcikova T, Januska J, Vojta P, Boday A, Vanickova P, et al. Newly designed 11-gene panel reveals first case of hereditary amyloidosis captured by massive parallel sequencing. J Clin Pathol. 2018 Aug;71(8):687–94. https://doi.org/10.1136/jclinpath-2017-204978
10. D'Aguanno V, Ralli M, Artico M, Russo FY, Scarpa A, Fiore M, et al. Systemic amyloidosis: a contemporary overview. Clin Rev Allergy Immunol. 2020 Dec;59(3):304–22. https://doi.org/10.1007/s12016-019-08759-4
11. Presnell SE, Schandl CA. Amyloidosis and unexpected death: a review of seven cases. Acad Forensic Pathol. 2016 Sep;6(3):543–54. https://doi.org/10.23907/2016.054
12. Reinés JB, Vera TR, Martín MU, Serra HA, Campins MM, Millán JM, et al. Epidemiology of transthyretin-associated familial amyloid polyneuropathy in the Majorcan area: son Llàtzer Hospital descriptive study. Orphanet J Rare Dis. 2014 Feb;9(29):29. https://doi.org/10.1186/1750-1172-9-29
13. Gertz MA, Benson MD, Dyck PJ, Grogan M, Coelho T, Cruz M, et al. Diagnosis, prognosis, and therapy of transthyretin amyloidosis. J Am Coll Cardiol. 2015 Dec;66(21):2451–66. https://doi.org/10.1016/j.jacc.2015.09.075
14. Beses C. Sans-Sabrarfen. Capítulo 30: Gammapatías monoclonales. Clasificación. Métodos de detección. Gammapatía monoclonal de significado incierto. Amiloidosis primaria. Hematología Clínica. Amiloidosis primaria. 5th ed. Madrid, Spain: Elsevier; 2007 Oct. pp 628–33.
15. Maurer MS, Elliott P, Comenzo R, Semigran M, Rapezzi C. Addressing common questions encountered in the diagnosis and management of cardiac amyloidosis. Circulation. 2017 Apr;135(14):1357–77. https://doi.org/10.1161/CIRCULATIONAHA.116.024438
16. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy diagnosis of cardiac transthyr-etin amyloidosis. Circulation. 2016 Jun;133(24):2404–12. https://doi.org/10.1161/CIRCULATIONAHA.116.021612
17. González LE, López SÁ, Garcia PP. Diagnóstico y tratamiento de la amiloidosis cardiaca por transtiretina. Progreso y esperanza. Rev Esp Cardiol. 2017 Nov;70(11):991–1004. https://doi.org/10.1016/j.recesp.2017.05.018

Summary of the case

1	**Patient (gender, age)**	Male, 34 year-old.
2	**Final diagnosis**	Hereditary FA with cardiac, gastrointestinal and neuropatic affection.
3	**Symptoms**	Weight loss, gastrointestinal manifestations, peripheral and autonomic neuropathy.
4	**Medications**	Prednisone 1mg/kg/day and melphalan 0.15mg/kg/day.
5	**Clinical procedure**	Histopathologic study of gastrointestinal and adipose tissue and peripheral nerve.
6	**Specialty**	Internal medicine