Author's response to reviews

Title: Chronic Diarrhea as the Presenting Feature of Primary Systemic AL Amyloidosis: a case report. Serendipity or delayed diagnosis?

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Author's response to reviews: see over
Cover Letter

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Re: Manuscript revision (Ms. ID 1052497516883382)

Dear Editor:

Thank you very much for your letter and for the accompanying reviewers’ comments on our manuscript. We are submitting a revised manuscript that incorporates the kind suggestions from the reviewers, in particular Dr. Marco Di Girolamo (Reviewer #2). A point-to-point response to the reviewers’ comments is listed below. We believe that the manuscript has been greatly improved and hope that the paper could be accepted for publication in your journal as a case report.

We are looking forward to your response.

Sincerely,

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Response to reviewers’ comments

Discretionary Revisions

Comment for the aim of the case report: “The manuscript could be interesting (point 2 of guidance for reviewers) only if it would be stressed that the ambiguous onset of the disease can bring to a delay of diagnosis, in spite of the presence of “red flag” of the disease that sometimes are not investigated. Moreover, the case report is interestingly instructive: it offers the opportunity to point out how sometimes a diagnosis is reached by using some available data without recognizing that already by the time of the disease onset were available other clinical findings This phenomenon is instructive to encourage doctors to better evaluation of all diagnostic elements as a whole (instrumental, laboratory, clinical and anamnestic data) For this reason I suggest to the authors that the title (and also the intention of the communication) might be better as follows: “Chronic diarrhea as the presenting feature of systemic AL amyloidosis: a case report. Serendipity or delayed diagnosis?”

Revision: Page 1, line 1-3. The title has been changed as suggested by the reviewer.
Comment for the etiology of chronic diarrhea: “It is necessary to study deeply the differential diagnosis with the other conditions of chronic diarrhea. A definite cause of diarrhea illness is often not identified. Chronic diarrhea is defined as diarrheal illness lasting for more than 4 weeks. Much more emphasis is needed to the differential diagnosis above all for the more frequent and rare causes of “secretory diarrhea” that are the more difficult diagnose. There are many causes of chronic diarrhea (chronic inflammatory, infections, ischemic colitis, malignancy, malabsorption and maldigestion syndromes, chronic watery diarrhea (osmotic, secretory). The differential diagnosis of secretory diarrhea should include infections, structural diseases, endocrinopathy and peptide-secreting tumors (tirotossicosi, VIPoma, carcinoid, gastrinoma)”

Revision: page 3, line 37-40; page 4, line 1-2. The differential diagnosis for secretory diarrhea has been rewritten, especially emphasizing the evaluation of endocrinopathies.

Comment: “How many years ago was performed echocardiography? Has never been previously reported the appearance of hypertrophic cardiomyopathy?”

Revision: page 3, line 20-22; The time point and echocardiographic result concerned by the reviewer were added.

Comment for the diagnosis of primary AL amyloidosis or secondary to multiple myeloma: “In the presentation is indicated that the patient showed a monoclonal gammopathy without evidence of any osteolytic lesions of the X-ray controls and 11.5% of bone marrow plasma cells. This clinical condition is more characteristic of a primary form of amyloidosis AL rather than a form of secondary amyloidosis plasma-cell myeloma associated. For this reason I think it is more appropriate to amend the text when it comes to "systemic amyloidosis associated with multiple myeloma" with the words "primary systemic AL amyloidosis””

Revision: The diagnosis for this patient has been changed to primary (systemic) AL amyloidosis in different parts of this case report.

Comment: “The diagnosis of amyloidosis must be confirmed by tissue typing fibril tissue deposit by immunochemistry. Many reasons confirm that: amyloid deposit in the gastrointestinal tract could be present in the primary and secondary amyloidosis. The symptoms and findings are nonspecific and resemble those of chronic inflammatory bowel disease and ischemic colitis. Secondary amyloidosis can be seen as a rare complication of Crohn's disease and ulcerative colitis. Special staining is necessary to show amyloid deposit, and the distinction between primary and secondary amyloidosis requires immuno-histochemistry. Only with such a method it is possible to avoid the risk (rare but significant) to give to a patient the therapy wrongly considering him affected by amyloidosis AL (of hematologic origin), whereas it is amyloidosis AA (secondary for example of a chronic flogistic disease of the bowel) or, more rarely amyloidosi TTR (due to a mutation of the transthyretin gene)”
Revision: Page 4, line 28-30; As suggested by the reviewer, immunohistochemical staining should be used to identify the type of protein deposits, but this method is not performed routinely in our hospital, due to some technical problems. We generally use potassium permanganate pretreatment as a screening test to differentiate AL and AA amyloidosis (Lab Invest. 1977 Mar; 36(3):274-81). And the final diagnosis for AL is always based on immunofixation for serum and/or urine.

Comment for the diagnostic delay: “Well talk about the diagnostic delay, but be careful about "rarity" of the presentation, especially if (in the case report describe that there were other diagnostic elements (hypertrophic heart disease, orthostatic hypotension, and paresthesias) "pathognomonic" of amyloid disease. In addition, the physician's delay: the delay in diagnosis of doctors is often due to non-specificity of symptoms and sometimes the inability to consider more symptoms seemingly unrelated to each other as an expression of the same clinical picture (red flags). In our case, hypotension, the hyperaesthesia, heart disease, hypertrophic CM). If taken together they would have perhaps allowed to reach faster to the final diagnosis. The diagnosis of amyloidosis cannot be entrusted to an isolated finding biopsy (which may be negative in a fair percentage of cases), but should be suspected and sought assiduously, especially if, after two years of diarrhea in the absence of other causes characteristic signs (blood pressure and heart disease, hypertrophic). It’s hard to argue that in two years from onset, while the amyloid fibrils continued to infiltrate the intestinal mucosa, had not caused other tissue damage”

Revision: page 6, line 10-31; The analysis for the diagnostic delay in this case has been rewritten, mainly inspired and directed by the highly informative suggestions provided by the reviewer.

Major Compulsory Revisions

Comment: “In the description of the case (2 years of diarrhea with weight loss of 35 pounds!) needs to be explained better the diagnostic procedure below, taking into account the possible diagnostic hypotheses formulated and not just merely list the imaging studies (CT and endoscopy). In history should be better indicated if the patient has arrived to the your observation only at the end of two years after the onset of diarrhea. If it happened just like that, it may indicate that "... it is unknown whether if in the previous period had never been observed (or investigated), postural hypotension, or if it was never highlighted proteinuria, the presence of a CM, hypertrophic cardiomyopathy-restrictive sensorimotor peripheral neuropathy, micturition disorders or buildings to face, macroglossia, events ecchymotic periorbital regions, etc. (all signs or symptoms that could be addressed to the clinical suspicion of amyloidosis)”

Revision: page 3, line 18-21; The conditions for previous medical referrals were added.

Comment: “In the description it seems that the diagnosis of amyloidosis was a serendipity ("... To our surprise ...") due to a lucky ileal biopsy, with no findings previously existing. It’s very
difficult to think that in the two previous years the amyloid fibrils have caused only the bowel involvement without other organ impairment. In our patient, hypertrophic cardiomyopathy, and orthostatic hypotension described represent two "red flags" of amyloid disease very likely present already for more than 12 months, although not noticed”

**Revision:** page 6, line 24-28; As suggested by the reviewer and already modified in the discussion part of our manuscript, the delayed diagnosis for this patient may be due to the un-recognition of the clinical signs or symptoms (as the orthostatic hypotension) that onset at different time points during his clinical course. While these signs and symptoms are actually decisive factors to make a correct diagnosis.

Ileal biopsy with an instructive suggestion can be regarded as a “serendipity” that a pathological data was get, which is highly suggestive for the correct diagnosis of this patient. Therefore, the title of this case report was also revised into “Chronic diarrhea as the presenting feature of systemic AL amyloidosis: a case report. Serendipity or delayed diagnosis?” as recommended by the reviewer.

**Response to editorial requirements**

**Requirement:** “Please remove the information that the patient is a teacher from the revised manuscript”

**Revision:** The information that the patient is a teacher has been deleted.

**Requirement:** “Request for copy editing”

**Revision:** Besides the revisions aforementioned, other modifications for the language were labeled in the revised manuscript, hoping to improve its rationality and fluency.