Reviewer's report

Title: Chronic Diarrhea as the Presenting Feature of Systemic Amyloidosis Associated with Multiple Myeloma: a case report

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Reviewer: Marco Di Girolamo

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Review of a Case report
Title : Chronic Diarrhea as the presenting feature of systemic Amyloidosis associated with multiple myeloma: a case report”

The case report submitted to BMC Gastroenterology fall under the category 2: “unexpected or unusual presentations of a disease”

My comments are divided in two categories:

Discretionary Revisions
I suggest the author consider the following :
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 ? “

Etiology of Chronic diarrhea

It is necessary to study deply 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
to 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 (tireotossicosi, VIPoma, carcinoide, gastrinoma,)

Pag 3
You describe: “The past medical history was remarkable for a diagnosed tuberculous pericarditis twenty years ago. No obvious abnormality was detected by echocardiography after half a year treatment with standard anti-tuberculosis regimen.

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

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"

Moreover (pag.4)
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 hemathologic 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).

[About this diagnostic problem it is shown below a useful reference "http://www.nejm.org/doi/full/10.1056/NEJMoa013354"

Misdiagnosis of Hereditary Amyloidosis as AL (Primary) Amyloidosis
Hereditary, autosomal dominant amyloidosis, caused by mutations in the genes encoding transthyretin, fibrinogen A

Hereditary, autosomal dominant amyloidosis, caused by mutations in the genes encoding transthyretin, fibrinogen A # chain, lysozyme, or apolipoprotein A-I, is thought to be extremely rare and is not routinely included in the differential diagnosis of systemic amyloidosis unless there is a family history.

Amyloidogenic mutations were present in 34 of the 350 patients (9.7 percent), most often in the genes encoding fibrinogen A # chain (18 patients) and transthyretin (13 patients). In all 34 of these patients, the diagnosis of hereditary amyloidosis was confirmed by additional investigations. A low-grade monoclonal gammopathy was detected in 8 of the 34 patients (24 percent).

Pag. 5 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 can not 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.

Major Compulsory Revisions

Pag. 2

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).

Pag. 3

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 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.