

Association of Secondary Amyloidosis with Common Variable Immune Deficiency and Tuberculosis

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This paper describes the first case of common variable immunodeficiency (CVID) and AA amyloidosis. A recently treated tuberculosis, and chronic inflammation induced by frequent respiratory tract infections, were thought to be responsible for the amyloidosis. No other reason for this condition could be detected. Although T cell dysfunction in some CVID patients has been reported, pulmonary tuberculosis is quite rare with this condition. Bacterial or viral agents or evidence in favour of intestinal tuberculosis, which would explain this patient's recurrent diarrhea, were not found. In this case, the response of the attacks of diarrhea to metranidazole and the histologic observation of extensive intestinal amyloid deposition, which is known to decrease intestinal motility, made us conclude that the diarrhea was associated with bacterial overgrowth. In this report, we discuss the association of CVID and tuberculosis to secondary amyloidosis and recurrent diarrhea.

Key Words: Common variable immunodeficiency, secondary amyloidosis, tuberculosis, diarrhea

INTRODUCTION

Common variable immunodeficiency (CVID) is a not uncommon disease which usually manifests in the second or third decade of life with recurrent bacterial infections and hypoglobulinemia.^{1,2} There is surprisingly, a high incidence of gastroin-

testinal diseases and chronic diarrhea, which is reported in as many as 30% of these patients. A microbial agent can be identified in fewer than half the cases and is most likely to be *Giardia lamblia* or bacterial overgrowth in the small bowel.³ Enteroviral infections may occur but they are not a major problem. Chronic diarrhea is one of the most common presentations of the disease and it can sometimes be quite troublesome. Although the diarrhea is usually infectious, it may be associated with Crohn's disease, gluten enteropathy, collagenous colitis, achlorhydria and pernicious anemia.^{4,6}

Recurrent bacterial infections during the course of CVID have been reported; however, the development of tuberculosis and secondary amyloidosis has not been reported until now. In this current case, the first patient in the literature with CVID and amyloidosis, who presented with recently worsened chronic diarrhea and sepsis, is described. A rare case of tuberculosis with CVID and their amyloid relationship is discussed.

CASE REPORT

A 28-year-old male was admitted to our hospital with a two-month history of diarrhea, abdominal pain, weight loss, fever, and fatigue. His medical history revealed 3 to 5 episodes of diarrhea each year and recurrent respiratory tract infections since the age of 14 years old. He had been successfully treated for postprimary cavitary pulmonary tuberculosis (acid-fast bacteria in smears

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of sputum and sputum culture positive for *Mycobacterium tuberculosis* in Lowenstein media) and had been given isoniazid (300 mg/day), rifampicine (600 mg/day), ethambutol (1.5 g/day) and pyrazinamide (2 g/day) for 2 months, followed by isoniazid and rifampicine for 10 more months, until 2 months prior to his hospitalization. His condition rapidly deteriorated with the above mentioned symptoms apparent 2 months after cessation of antituberculosis therapy.

Physical examination revealed a severely malnourished male with a temperature of 39°C; blood pressure 100/60 mmHg; and a heart rate of 96/min. Abdominal examination revealed increased bowel sounds and slight abdominal tenderness. Laboratory studies disclosed: hemoglobin, 14.3 g/dL; WBC, 15,600/ μ L; platelets, 308,000/ μ L; ESR, 60 mm/h; CRP, 41.4 mg/dL (normal 0-5); total protein, 5.1 g/dL; and albumin, 2.7 g/dL. Other biochemical data was normal. Urinalysis revealed 4+ proteinuria with oval fat bodies in the sediment. Creatinine clearance was 93 mL/min and proteinuria was 9 g/d. Serum immunoglobulins were as follows: IgG, 168 mg/dL (normal 800-1700); IgM, 8.95 mg/dL (normal 50-320); IgA, 10.2 mg/dL (normal 85-450); and, IgE, 28.7 IU/mL (normal 0-100). C3 complement was 54.3 mg/dL (normal 50-90). Anti-gliadine IgA and IgG were both negative. CD4/CD8 ratio, CD3, CD56 were normal and tuberculin skin test was positive (17 mm induration). Neutrophil function tests (chemotaxis, phagocytosis, oxidative burst) were within normal limits. Chest X-ray and ECG were normal.

Cultures of blood and urine were negative. Numerous erythrocytes and leucocytes were seen in the stool specimen, but stool cultures for *Salmonella*, *Shigella* and *Campylobacter* were negative. Toxin A was negative in the stool. Serologies for HIV, HBV, HCV were negative. Anti-HSV, anti-EBV and anti-CMV IgM's were also negative.

Thoracic CT revealed old fibrotic scars in the upper lobes of both lungs, suggesting healed tuberculosis. Abdominopelvic CT was normal. On radiologic examination of the small bowel, there was dilatation and increased mucosal thickness of valvula conniventes. Gastroduodenoscopy was normal; multiple biopsies were obtained and duodenal aspiration was performed. Rectosigmoi-

doscopy was nondiagnostic. Histologic examination of esophageal, duodenal, colon (Fig. 1) and gastric (Fig. 2) biopsies revealed extensive, subepithelial, Congo red positive amyloid deposition. Disappearance of these after adding KMnO₄ suggested AA amyloidosis, also confirmed by immunohistochemical staining. In addition, the four currently identified mutations of MEVF gene on exon 10, associated with familial Mediterranean fever (FMF) -which are M694V, M694I, M680I, V726A,- were negative.

Ciprofloxacin (200 mg, bid, i.v.) and metronidazole (500 mg, bid, i.v.) were commenced. The patient's clinical condition started to improve within a few days and returned to normal at 3 weeks. The antibiotics were then discontinued and the patient was discharged. Two weeks later,



Fig. 1. Massive amyloid deposition beneath the surface epithelium (Congo-red \times 200).

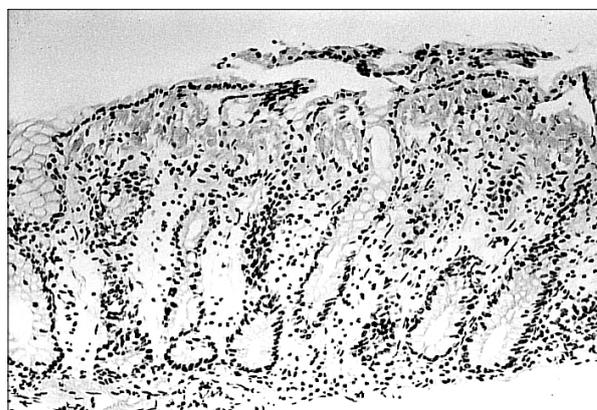


Fig. 2. Extensive amyloid deposition is visible among the crypts of the lamina propria and in the deep mucosa. (Congo-red \times 200).

diarrhea with 3-4 bowel movements/day developed, and repeated diagnostic tests revealed no specific cause. Metronidazole was recommended for 3 further months during which the patient's diarrhea disappeared and he put on 18 kg but hypogammaglobulinemia and nephrotic-range proteinuria persisted. Later, colchicine 1.5 mg/day was administered to hopefully control proteinuria.

At the end of the third year of follow-up; the patient was still using colchicine and also metronidazole (500 mg, bid, p.o.) for one week every month or in the case of >3 mushy stools/day lasting >3 days. The control gastroscopy and rectosigmoidoscopy were normal: biopsies showed AA amyloid infiltration. Although the patient had hypogammaglobulinemia, his condition did not worsen except for recurrent upper respiratory tract infections, a recent acute attack of chronic otitis media, and chronic recurrent diarrhea. The patient's creatinine clearance was normal, but the proteinuria was still in the nephrotic range.

DISCUSSION

Pulmonary tuberculosis in patients with CVID was reported as a rare entity in the literature.⁷ Whether this concurrent disease pairing is just coincidence or due to a defect in T-cell function is not clear. Because of the high prevalence of tuberculosis (0.38%) in the general population in Turkey (Data from the Ministry of Health, 1992), we cannot exclude the possibility of coincidence. T-cell dysfunction may be present in up to half of CVID cases.^{3,8} In this case, although the presence of tuberculosis might still have been related to a T-cell functional defect which accompanies CVID, normal lymphocyte function tests and a positive tuberculin skin test, suggest no T-cell dysfunction.

Although recurrent infections are common in CVID,^{3,7-9} no other reported case of secondary amyloidosis accompanying CVID, could be found. Renal amyloidosis secondary to pulmonary tuberculosis is fairly common (3.6-50%).^{10,11} In this case, it is difficult to determine the duration of the subclinical pulmonary tuberculosis. However, the development of cavitation suggests that the patient has had a long period of silent inflammation which may have been a reason for secondary

amyloidosis. Therefore, although tuberculosis may not be the only possible cause of amyloidosis in this case, it is easy to comment on whether other frequent infections had some additive effect on the inflammatory response. In Turkey, one of the possible causes of amyloidosis might have been FMF, but in our patient there was no history suggestive of FMF and none of the described FMF gene mutations were present.

In this case, one possible cause for recurrent diarrhea may have been intestinal tuberculosis. Although intestinal tuberculosis accompanies cavitory tuberculosis and positive sputum smears, with a much higher incidence than in noncavitory tuberculosis,¹² worsening of the diarrhea since the patient's childhood in a continuous fashion 2 months after cessation of antituberculosis therapy, might prove that tuberculosis was probably not the cause of the diarrhea. Also, there were no signs suggestive of intestinal tuberculosis, both radiologically and endoscopically. Furthermore, *Mycobacterium tuberculosis* could not be seen in direct examination of, and specific cultures of, the stool.

There is an increased incidence of Crohn's disease in CVID¹³ and this may have been another cause for this patient's diarrhea. As in intestinal tuberculosis, amyloidosis secondary to Crohn's disease is also rare in the literature.^{14,15} In this case, increased mucosal thickness of the valvula conniventes, visible with a barium meal, were suggestive of Crohn's disease. However, gastrointestinal system biopsies did not reveal any histologic findings supporting granulomatous bowel disease.

Viral etiologies for diarrhea were excluded by negative serology and by the absence of inclusion bodies in the biopsy specimens. Also, colchicine, which was used in this patient, could possibly cause mild diarrhea. Colchicine was shown to have promising results in experimental cases of secondary amyloidosis but it is not that effective clinically.¹⁶ In this patient however, it was introduced after the onset of diarrhea.

In the case of gastrointestinal amyloidosis, decreased gastrointestinal motility causes bacterial overgrowth, bile acid deconjugation and consequently, diarrhea, steatorrhea and severe malabsorption.¹⁷ In this case, another possible cause of

diarrhea is giardiasis frequently seen in CVID. The resolution of symptoms with oral metronidazole in each attack of diarrhea, suggests that either bacterial overgrowth or giardiasis were responsible for the diarrhea. However, giardia was not seen in stool analysis, duodenal biopsies or duodenal aspiration which suggests bacterial overgrowth. In addition, Whipple's disease can also present with the same symptomology and responds to broad-spectrum antibiotics but has frequent recurrence of symptoms. However, the intestinal biopsy specimens in our case did not reveal the presence of any PAS positive microorganisms.

In this case, extensive amyloid infiltration and incomplete local defences inducing overgrowth are the probable causes of diarrhea. It is unusual to see tuberculosis with CVID. However, the coincidence of this occurring, in a country endemic for tuberculosis, is not surprising. Secondary amyloidosis in this case was most probably due to the additive effects of tuberculosis and recurrent bacterial infections during the course of CVID.

REFERENCES

1. Sneller MC, Strober W, Eisenstein E, Jaffe JS, Cunningham-Rundles C. NIH conference. New insights into common variable immunodeficiency. *Ann Intern Med* 1993;118:720-30.
2. Hermans PE, Diaz-Buxo JA, Stobo JD. Idiopathic late onset immunoglobulin deficiency. Clinical observations in 50 patients. *Am J Med* 1976;61:221-32.
3. Cunningham-Rundles C. Clinical and immunologic analysis of 103 patients with common variable immunodeficiency. *J Clin Immunol* 1989;9:22-33.
4. Washington K, Stenzel TT, Buckley RH, Gottfried MR. Gastrointestinal pathology in patients with common variable immunodeficiency and X-linked agammaglobulinemia. *Am J Surg Pathol* 1996;20:1240-52.
5. Byrne MF, Royston D, Patchett SE. Association of common variable immunodeficiency with atypical collagenous colitis. *Eur J Gastroenterol Hepatol* 2003;15:1051-3.
6. Tanus T, Levinson AI, Atkins PC, Zweiman B. Polyautoimmune syndrome in common variable immunodeficiency. *J Intern Med* 1993;234:525-7.
7. Yocum MW, Kelso JM. Subspecialty clinics: Common variable immunodeficiency: the disorder and treatment. *Mayo Clin Proc* 1991;66:83-96.
8. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol* 1999;92:34-48.
9. Ament ME, Rubin CE. Relation of giardiasis to abnormal intestinal structure and function in gastrointestinal immunodeficiency syndromes. *Gastroenterology* 1972;62:216-26.
10. Bely M, Apathy A. Disease modifying factors in chronic polyarthritis. Correlations among systemic vasculitis, secondary amyloidosis, septic infections and occurrence of miliary epithelioid-cell granuloma. A review of autopsies. *Zentralbl Pathol* 1993;139:51-60.
11. Urban BA, Fishman EK, Goldman SM, Scott WW Jr, Jones B, Humphrey RL, et al. CT evaluation of amyloidosis: spectrum of disease. *Radiographics* 1993;13:1295-308.
12. Hamer DH, Gorbach SL. Infectious diarrhea and bacterial food poisoning. In: Feldman M, Scharsschmidt BF, Sleisenger MH, editors. *Gastrointestinal and liver disease*, 6th ed. Philadelphia: W.B. Saunders Company; 1998. p.1594-632.
13. Kagnof MS. Immunology and inflammation of the gastrointestinal tract. In: Feldman M, Scharsschmidt BF, Sleisenger MH, editors. *Gastrointestinal and liver disease*. Sixth ed. Philadelphia: W.B. Saunders Company; 1998. p.19-48.
14. Gries E, Singer MV, Goebell H. Amyloidosis in Crohn disease. Case reports and review of the literature. *Med Klin (Munich)* 1989;84:65-71.
15. Friedman S, Janowitz HD. Systemic amyloidosis and the gastrointestinal tract. *Gastroenterology Clin North Am* 1998;27:595-614.
16. Cathcart ES. Amyloidosis. In: Kelley WN, Harris ED, Jr., Ruddy S, Sledge CB, editors. *Textbook of Rheumatology*. Philadelphia: W.B. Saunders Company; 1993. p.1413-28.
17. Feurle GE. Pathophysiology of diarrhea in patients with familial amyloid neuropathy. *Digestion* 1987;36:13-7.