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Single Case

Systemic AA Amyloidosis Secondary to Metastatic Renal Cell Carcinoma in a Hemodialysis Patient with Intractable Diarrhea

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Keywords
Amyloidosis · Renal cell carcinoma · Diarrhea · Hemodialysis

Abstract
We describe an autopsied case of systemic AA amyloidosis secondary to metastatic renal cell carcinoma presenting intractable diarrhea. Severe diarrhea was the major symptom for the diagnosis of AA amyloidosis. No renal symptoms which are common in AA amyloidosis secondary to renal cell carcinoma were shown because hemodialysis following bilateral nephrectomy had already been started 9 years before. Treatment against metastatic tumors as a solution of AA amyloidosis could not be performed because of bad performance status and the patient died 5 months after the diagnosis. Autopsy findings revealed that AA amyloid deposition was seen in multi-organs including the intestine. The metastatic tumors were histologically compatible as metastasis of renal cell carcinoma. There was no other cause of chronic inflammation such as inflammatory arthritis. We concluded that chronic inflammation provoked by the metastatic tumors of renal cell carcinoma was a major cause of systemic AA amyloidosis. Intestinal AA amyloidosis with malabsorption was the cause of death. Clinicians should keep it in mind that solid organ malignancy can be a cause of AA amyloidosis and renal cell carcinoma is the most common carcinomatous cause. This case is particularly instructive in that progression of amyloidosis may be missed in hemodialysis patients with anuria and that gastrointestinal symptoms can be the primary indicators of systemic amyloidosis. Endoscopic examination including biopsy is important for the diagnosis and early treatment of amyloidosis.

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Introduction

Systemic amyloidosis is caused by aggregation and deposition of amyloid fibril in various tissues and multi-organs. AA amyloidosis is one of the major types of systemic amyloidosis in which the serum amyloid A (SAA) protein becomes a precursor protein due to long-term inflammation. As for the cause of AA amyloidosis, it was reported that the most frequent underlying disorder was inflammatory arthritis such as rheumatoid arthritis, and a malignant disease was one of the rare causes [1]. Renal cell carcinoma was reported to be the most common carcinomatous cause of amyloidosis [2, 3]. It was also reported that renal symptoms such as proteinuria and hematuria were the most frequent symptoms of AA amyloidosis patients with renal cell carcinoma [4]. Herein, we report a case of systemic AA amyloidosis secondary to metastatic renal cell carcinoma lacking renal symptoms due to post-bilateral nephrectomy. Severe diarrhea was a major symptom which led to the diagnosis of AA amyloidosis.

Case Report

A 62-year-old Japanese man undergoing hemodialysis developed intractable diarrhea and was hospitalized in April 2019. His general condition was bad and performance status (PS) was scaled as grade 3. He had undergone bilateral nephrectomy for bilateral renal cell carcinomas; hemodialysis was started in 2010. Metastatic tumors of renal cell carcinoma had been identified at the left rib and the right lung in 2014 and 2018, respectively. The former had been treated by radiation therapy and the latter had been observed. The blood test revealed elevated C-reactive protein (6.51 mg/dL), elevated SAA (253 μg/mL), and hypoalbuminemia (1.8 g/dL). Several years of chronic elevation of C-reactive protein (ranged about 2.0–8.0 mg/dL) had been diagnosed by the hemodialysis clinic before this hospitalization. Computed tomography revealed the known metastatic tumors (rib, lung) and intestinal edema (Fig. 1a, b). This finding was particularly evident at the ileocecum (Fig. 1c). Lower endoscopic examination revealed scattered erosions at the descending and sigmoid colon (Fig. 1d). The oral side beyond splenic flexure could not be evaluated endoscopically because the sigmoid colon was easily extended and the endoscope could not pass through the splenic flexure. The possibilities of bacterial or viral infection, drug-induced enterocolitis, and inflammatory bowel disease were ruled out by endoscopic findings and other clinical information (e.g., laboratory data, fecal culture, contents of medication). To investigate the cause of intractable diarrhea, biopsies from colonic erosions were done and hematoxylin and eosin and direct fast scarlet staining finding showed amyloid deposition in the submucosal layer of the colonic mucosa with erosion (Fig. 2a, b). Immunohistochemically, the amyloid protein was positive for SAA (Fig. 2c) and negative for κ and λ-light chain, β2 microglobulin, prealbumin (data are not shown). Based on these findings, intestinal AA amyloidosis was suspected as the cause of intractable diarrhea. Chronic inflammation provoked by the metastatic tumors of renal cell carcinoma was suspected as a major cause of AA amyloidosis because no other source of inflammation was detected. Although the treatment against metastatic tumors was considered as a solution of AA amyloidosis, it could not to be performed because of bad PS with malnutrition of the patient. Even though he was observed with the best supportive care, he died in September 2019.

Clinically, malabsorption caused by intestinal AA amyloidosis was suspected as a major cause of his death. However, the histological findings of the ileocecum of which edema was particularly evident could not be gained because the endoscope could not reach there.

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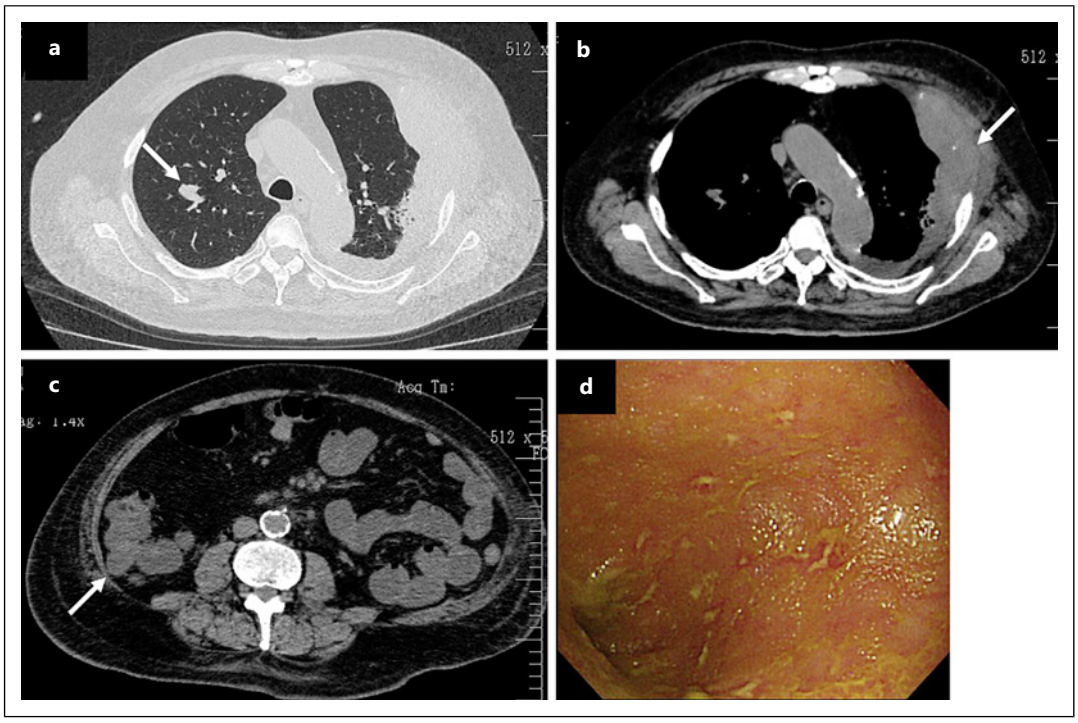

Fig. 1. Findings of CT and lower endoscopic examination. **a** The nodule of the right lung is regarded as a metastasis of renal cell carcinoma. **b** The tumor of the left rib that was treated by radiation therapy in 2014 is also regarded as a metastasis of renal cell carcinoma. **c** The edema of the intestine is particularly evident at the ileocecum. **d** Scattered erosions are seen at the descending and sigmoid colon.

Moreover, tumors of his left rib and lung had not been evaluated histologically, although they seemed to be clinically compatible as metastasis of renal cell carcinoma. Therefore, the autopsy was conducted for precise pathological assessment.

Autopsy findings revealed severe macroscopic inflammation with erosions and ulcers at the ileocecum (Fig. 3a). Microscopically, the amyloid deposition was seen at the submucosal layer including perivascular areas under the erosions. Furthermore, systemic amyloid deposition was seen in other organs (e.g., heart, liver, spleen, lung, thyroid, pancreas, bladder, prostate, small and large intestines). These amyloid proteins showed the same immunohistochemical findings as the biopsied specimens (positive for SAA, negative for κ and λ-light chain, β2 microglobulin, pre-albumin) (Fig. 3c–e). These findings indicated systemic AA amyloidosis. Diffuse amyloid deposition in the intestine including the ileocecum caused malabsorption and intractable diarrhea. In addition to the recognized tumors of the rib and lung, the autopsy also revealed other macroscopic tumors of the lymph node and stomach. All these tumors consisted of clear cell carcinoma and were compatible as metastasis of renal cell carcinoma histologically (Fig. 3b). There was no other cause of chronic inflammation. From these autopsy findings, we concluded that chronic inflammation provoked by the metastatic tumors of renal cell carcinoma was a major cause of systemic AA amyloidosis. Intestinal AA amyloidosis led to malabsorption which was the cause of death.

Discussion

To the best of our knowledge, this is the first report about systemic AA amyloidosis secondary to metastatic renal cell carcinoma in a hemodialysis patient. Since hemodialysis after bilateral nephrectomy resulted in anuria, the chance of renal symptoms which are the

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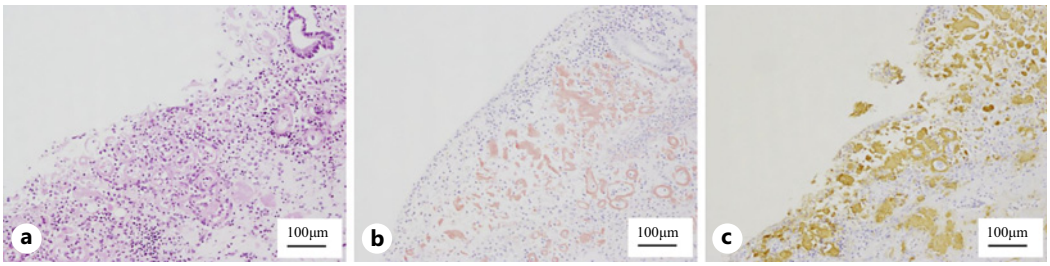

Fig. 2. Histological findings of the biopsied specimens from the colonic erosion. **a** Acidophilic and homogeneous amorphous material is identified in the submucosa (H&E staining). **b** This material shows positive staining for DFS and is compatible as an amyloid protein. **c** Immunohistochemically, the amyloid protein shows positive staining for SAA. DFS, direct fast scarlet; H&E, hematoxylin and eosin.

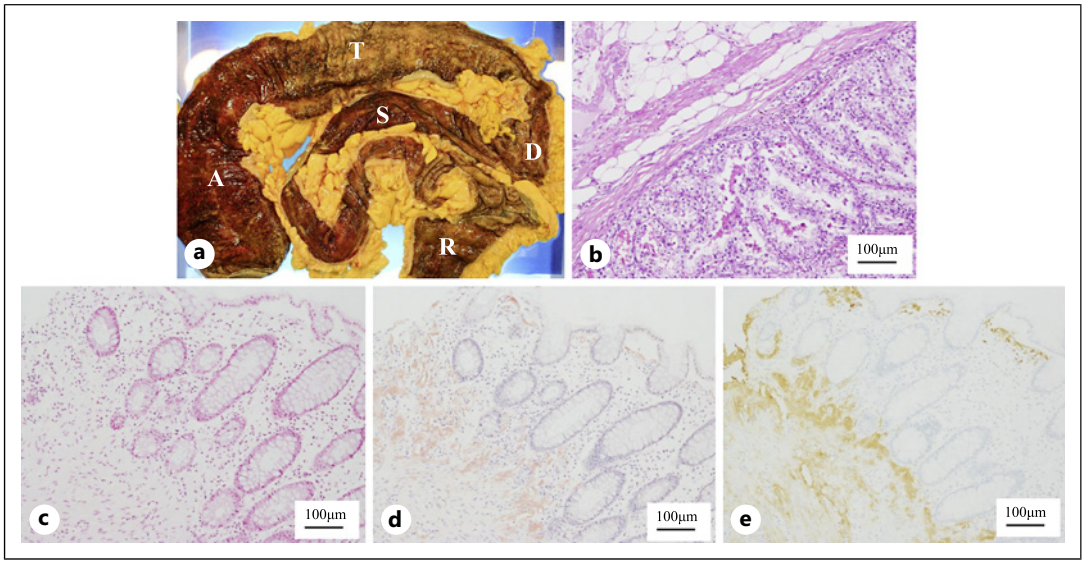

Fig. 3. Finding of autopsy. **a** Severe inflammation such as erosions, ulcers are seen at the large intestine macroscopically. A, ascending; T, transverse; D, descending; S, sigmoid; R, rectum). These findings are evident at the ileocecum. **b** The left rib tumor consists of clear cell carcinoma and is histologically compatible as metastasis of renal cell carcinoma. **c–e** The histological findings of erosion of large intestine show the same pattern as the biopsied specimens. Amyloid deposition in the submucosal layer is shown under the erosions. This amyloid protein is positive staining for SAA (**c** H&E; **d** DFS; **e** SAA). DFS, direct fast scarlet; H&E, hematoxylin and eosin.

most frequent symptom of the patient of AA amyloidosis with renal cell carcinoma was lost. Severe diarrhea was a major symptom which led to the diagnosis of AA amyloidosis. This case is instructive in that progression of amyloidosis may be missed in hemodialysis patients with anuria and that gastrointestinal symptoms can be the primary symptoms of systemic AA amyloidosis.

It was reported that AA amyloid tended to deposit on the lamina propria mucosae and submucosal layer in a macular or perivascular form whereas AL amyloid tend to deposit in the submucosal layer and/or muscularis propria as a mass [5]. Vascular deposition was reported to induce ischemic changes in the intestinal mucosa, such as surface denudation and ulceration [6]. Occurrence of diarrhea and malabsorption was reported to be more frequent in AA amyloidosis cases compared to other amyloidosis cases [7]. Both histological and clinical

findings of our case were coincidence with that reported in these previous reports. Chronic intestinal ischemic changes caused by perivascular AA amyloid deposition were thought to be the main cause of diarrhea.

Some case reports about systemic AA amyloidosis with abdominal symptoms secondary to primary or metastatic renal cell carcinoma were reported [4, 8–12]. These symptoms were reported to improve after nephrectomy or chemotherapy in almost all cases. In our case, chemotherapy against metastatic tumors could not be performed because of bad PS with malnutrition of the patient. Although this patient had mild diarrhea before this hospitalization, the cause of diarrhea had not been investigated in the hemodialysis clinic. The urologists had planned to start chemotherapy after improvement of this mild diarrhea. Unfortunately, the relation between a symptom of diarrhea and metastatic renal cell carcinomas could not identified by the urologists until this hospitalization. The endoscopic examination including biopsy was important for the diagnosis of intestinal AA amyloidosis. Earlier consultation with a gastroenterologist might have led to an earlier diagnosis of AA amyloidosis and a better prognosis.

In conclusion, it is important to recognize that solid organ malignancy can be a cause of AA amyloidosis and renal cell carcinoma is the most common carcinomatous cause. Since dialysis patients lack symptoms of renal amyloidosis, gastrointestinal symptoms such as diarrhea can be an important clue and an endoscopic examination including biopsy is important for the early diagnosis and treatment of AA amyloidosis. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531066).

Statement of Ethics

All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written Informed consent was obtained from the patient's wife prior to publication of the report and any accompanying images. She was permitted to provide consent on behalf of the patient. Ethical approval was not required for this study in accordance with local and national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.E. wrote the draft of this manuscript. H.E., N.O., and S.M. managed the patient. Y.N. analyzed the pathological findings. All the authors have read and approved the final version of the manuscript.

Data Availability Statement

All data analyzed during the study are included in this article and its online supplementary material. Inquiries can be sent to the corresponding author.

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