the p53 protein, as detected by immunohistochemistry, has been demonstrated by Biernat *et al* in the carcinomatous component of three cases of malignant eccrine spiradenoma.⁴ The authors found no positive staining in cases of typical benign eccrine spiradenoma or in the benign areas of the malignant tumours. Interestingly, in the present case, there was definite positive nuclear staining with DO-7 in the morphologically benign component as well as in the carcinomatous and sarcomatous areas. Biernat *et al* considered that accumulation of p53 protein may play an important role in the progression from benign to malignant eccrine spiradenoma, a hypothesis that would be supported by the immunohistochemical findings in the present case.

The neoplasm we describe contained recognisable epithelial and mesenchymal elements, both of which were malignant and thus qualified for the designation carcinosarcoma. Carcinosarcoma has occasionally been described as a primary tumour within the skin, without a pre-existing benign sweat gland neoplasm.⁵ Most reported cases have consisted of areas of basal cell carcinoma (with or without squamous elements) admixed with sarcomatous elements. It is probable that the mesenchymal component in cases of carcinosarcoma represents sarcomatous metaplasia in malignant epithelial cells. Ultrastructural examination in the present case did not reveal any evidence of epithelial differentiation in the

sarcomatous areas. A prominent finding was the presence of intracytoplasmic lumina in the typical and carcinomatous areas. Intracytoplasmic lumina have been identified in other ultrastructural studies of eccrine spiradenoma.⁶

It is difficult to predict the prognosis of carcinosarcoma developing in eccrine spiradenoma as so few cases have been reported. Of the cases described by McKee *et al*,³ one patient died with pelvic and hepatic metastases within two years of diagnosis. The second patient remained alive and well 10 years following diagnosis and local resection. The rapid development of nodal and pulmonary metastases in the present case suggests an aggressive behaviour. It is of interest in the present case that the morphology of the nodal metastases mirrored that of the primary tumour with recognisable carcinomatous and sarcomatous components.

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β_2 Microglobulin haemodialysis related amyloidosis: distinctive gross features of gastrointestinal involvement

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Abstract

Two cases of β_2 microglobulin amyloidosis following long term haemodialysis found during necropsy are reported. The patients were 59 and 65 year old Japanese men, respectively. In both cases, systemic distribution of β_2 microglobulin amyloid deposits was observed. The gastrointestinal tract including the stomach, small intestine, and colon showed the distinctive gross feature of rippled appearance, which was characterised by serosal wrinkles along the muscle layer arrangement. These areas were confirmed to contain deposits of β_2 microglobulin in the muscularis propria. Although the outline of the muscle layers was preserved, most muscle fibres, encircled by the amyloid deposits,

were atrophic or had disappeared microscopically. In neither case could a definite diagnosis of amyloidosis be made while the patient was alive. Interestingly, the oesophagus presented less involvement compared to the remainder of the gastrointestinal tract. In comparison with the AA or AL type of amyloidosis, β_2 microglobulin haemodialysis related amyloidosis showed a rippled appearance of the serosal rather than mucosal changes, which may explain the difficulty in diagnosing amyloid deposits using biopsies of the gastrointestinal tract.

(*J Clin Pathol* 1997;50:873-875)

Keywords: β_2 microglobulin; amyloidosis; haemodialysis; gastrointestinal tract; stomach; small intestine; colon

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Accepted for publication
15 July 1997

Figure 1 Case 1: (A) Gross appearance of the serosal surface of the stomach showing a typical ripple appearance. (B) Serosal surface of the colon showing regular wrinkles along the muscle layer arrangement.

Amyloidosis in patients who have undergone long term haemodialysis particularly involves the osteoarticular system, and in such cases the principal protein component has been noted to be β_2 microglobulin, which is not removed by conventional haemodialysis. In addition, systemic amyloid deposits of β_2 microglobulin involving the gastrointestinal tract, liver, and lung have recently been described in cases of haemodialysis related amyloidosis.¹⁻⁵ One of the recent reports described the splenic resistance to amyloid deposition in β_2 microglobulin derived amyloidosis, although the reason was unknown.⁵ No distinctive gross feature has been reported concerning the gastrointestinal involvement by β_2 microglobulin, although amyloid deposits have been detected microscopically, mainly in the muscularis propria.^{6,7} We describe two cases of β_2 microglobulin haemodialysis related amyloidosis found at necropsy, and highlight the distinctive gross features of the gastrointestinal involvement compared with other chemical types of amyloid protein.

Case 1

A 59 year old Japanese man had been diagnosed with renal failure caused by multiple renal cysts 15 years previously, and haemodialysis had been started one year later. He was

referred to our hospital because of malabsorption possibly due to deposition of amyloid; however, biopsies of the stomach and rectum were negative for amyloid deposition. The serum β_2 microglobulin level was raised. Although steroids provided transient relief of gastrointestinal symptoms, the patient died from heart failure complicated with pneumonia; necropsy was performed.

PATHOLOGICAL FINDINGS

Macroscopically, the heart was hypertrophied and fibrous pleuritis was noted. Both kidneys were severely atrophic and acquired cystic kidney was observed. In the gastrointestinal tract, the stomach, small intestine, and colon showed thickened walls, and the cut surface was yellow. The serosa of the gastrointestinal tract presented a rippled appearance characterised by regular wrinkles, typically with yellow streaks, along the muscle layer arrangement (fig 1).

Microscopically, amyloid deposits were found mainly around the veins in the heart, lung, diaphragm, stomach, small intestine, colon, pancreas, adrenal gland, kidney, testis, prostate, and mesentery. Amyloid deposits were also noted in the muscle layer in the heart, stomach, small intestine, colon, gall bladder, prostate, and urinary bladder. In the gastrointestinal tract, diffuse amyloid deposition was seen mainly in the stomach in the outer longitudinal muscle layer, as well as in the small intestine and colon in both the inner circular and outer longitudinal muscle layers. Foreign body-type multinucleated giant cells were observed in the stomach, small intestine, and colon. They varied in distribution and number according to the organ. Although the outline of the muscle layers of the gastrointestinal tract was preserved, most muscle fibres, encircled by the amyloid deposits, were atrophied or had disappeared. Therefore, the amyloid deposition was located within the stroma.

Amyloid deposits were confirmed by Congo red stain, which showed characteristic green birefringence on polarisation microscopy. Immunohistochemically, P component and β_2 microglobulin were also positive, and amyloid A, prealbumin, and κ and λ light chains were negative.

Figure 2 Serosal surface of the stomach from case 2 showing a rippled appearance.

Case 2

A 65 year old Japanese man who had had haemodialysis for 18 years was referred to our hospital because of appetite loss and nausea. Gastrointestinal symptoms were not improved and their cause could not be detected despite investigation by endoscopy and abdominal ultrasound. He died of respiratory failure due to pneumonia three months after admission; necropsy was performed.

PATHOLOGICAL FINDINGS

Macroscopically, the kidneys were atrophic and acquired cystic kidneys were observed. In addition, renal cell carcinoma ($3.0 \times 2.2 \times 2.0$ cm) was noted. Cardiac hypertrophy and bronchopneumonia were found. Microscopically, as in case 1, amyloid deposits were observed in many organs, such as the tongue, submandibular gland, thyroid, heart, lung, diaphragm, oesophagus, stomach, small intestine, colon, liver, pancreas, gall bladder, adrenal gland, and kidney.

The macroscopic findings for the gastrointestinal tract were almost the same as for case 1. Wrinkles along the muscle layer arrangement—that is, serosal rippled appearance, was observed in the stomach, small intestine, and colon (fig 2). Microscopically, amyloid deposits were found mainly in the outer longitudinal muscle layer in the stomach, inner circular muscle layer in the small intestine, and both the inner circular and outer longitudinal muscle layers in the colon, which showed diffuse distribution. Multinucleated giant cells were also noted in the stomach, small intestine, and colon, which varied in distribution and number according to the organ. The amyloid was confirmed to be β_2 microglobulin derived by Congo red stain as well as by immunohistochemical staining of P component and β_2 microglobulin.

Discussion

β_2 Microglobulin haemodialysis related amyloidosis was first characterised by the involvement of the osteoarticular system, but it then became clear that extra-osteoarticular manifestations could cause serious complications.^{2,8} Therefore, β_2 microglobulin haemodialysis related amyloidosis is thought to be a generalised disease, that begins with osteoarticular involvement with extra-osteoarticular symptoms sometimes appearing as a late complication.⁹

Clinically, deposition of amyloid in the gastrointestinal tract may cause various symptoms because of ulceration, diarrhoea, malabsorption, haemorrhage, and protein loss,¹⁰ and the rectal biopsy may be diagnostic. However, the gastrointestinal involvement of amyloidosis differs according to the chemical types of amyloid protein.^{6,7} Compared with the amyloid deposits in arterioles and arteries in AA or AL type amyloidosis, β_2 microglobulin amyloid deposits are mainly observed in the muscularis propria.^{6,7} In addition, multinucleated cells are sometimes found.⁷ In our two cases, the amyloid deposits in the stomach, small intestine, and colon were situated in the muscularis propria in addition to the blood vessels, and

foreign body-type multinucleated giant cells were also observed. Although the outline of the muscle layers was preserved, the actual location of the amyloid deposits was the stroma and not the muscle fibre itself. Most muscle fibres were atrophic and had disappeared, and they were encircled or replaced by amyloid deposits. Interestingly, the oesophaguses in our patients were somewhat resistant to amyloid deposits compared with other parts of the gastrointestinal tract. Amyloid deposits were seen in the walls of the blood vessels of the oesophagus in case 2, but to a mild degree.

Recently, absence of splenic involvement in β_2 microglobulin haemodialysis related amyloidosis has been reported by Gal *et al*,⁵ although splenic involvement is common in other types of generalised amyloidosis and AA-type amyloidosis. Our findings in these cases confirm their finding as there was no splenic involvement of β_2 microglobulin amyloid, although the reason is unknown.

Clinically, β_2 microglobulin amyloidosis may manifest as severe delay in transit time and dilatation of the small and large intestine.⁶ However, so far no characteristic gross feature has been reported. Our observations indicate that the gross feature of the rippled appearance of the serosa is characteristic of the gastrointestinal involvement of β_2 microglobulin haemodialysis related amyloidosis. In addition, amyloid deposits of the stomach tend to be located mainly in the outer longitudinal layer, and those of the colon in both the inner circular and outer longitudinal muscle layers. Because of this muscle layer distribution of the amyloid deposits it is more difficult to diagnose the gastrointestinal involvement of β_2 microglobulin amyloidosis by endoscopic biopsy compared with AA or AL type amyloidosis. Scirrhus carcinoma of the stomach or corrosive gastritis may show the rippled appearance of the serosa; however, it shows irregular wrinkles and histological massive desmoplasia or fibrosis, neither of which is seen in β_2 microglobulin amyloidosis.

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