Surgical complications of amyloid disease

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Summary: The case of a man with primary systemic amyloidosis without myelomatosis and long-term survival is described. The patient has had major surgical complications from large amyloid deposits in the colon, dorsal spine and peritoneal cavity. The patient remains well 14 years after diagnosis.

Introduction

Systemic amyloidosis (AL) is an uncommon disorder¹ which is associated with an immunocyte dyscrasia in up to 25–50% of cases.^{2,3} Systems commonly involved are those of the heart, tongue, gastrointestinal tract, nerves and skin.³ It is an inexorably progressive disorder that is almost invariably fatal. Treatment remains unsatisfactory and death most frequently follows renal failure or a cardiac event.⁴ The median survival of patients with associated myeloma is 4 to 9 months and 12 to 15 months in those without myeloma.^{3,5} The overall 5-year survival rate is 20% or less¹⁻³ but is mostly dependent upon the main presenting symptom complex. Patients presenting with peripheral neuropathy have an estimated 5-year survival rate of 50% compared to only 20% in those presenting with nephrotic syndrome and there are no 5-year survivors amongst those presenting with cardiac involvement.³

Complications of the disorder may sometimes be relieved by surgery, although most of the indications are uncommon. Dysphagia may be due to macroglossia or oesophageal dyskinesia, and nasogastric or gastrostomy feeding is sometimes indicated.^{3,5} Laparotomy may be required in the management of obstruction or perforation of the bowel, or for gastrointestinal haemorrhage, which may be severe.⁶ Pseudo-obstruction has also been seen associated with amyloidosis.⁷ Splenectomy may be required for spontaneous rupture of the spleen⁸ or in the management of haemorrhagic diathesis associated with factor X deficiency.⁵ Deposits in the tracheobronchial tree may require bronchoscopy and curettage for haemorrhage, and may occasionally be surgically excised if

localized.³ Fractures may occur through bone deposits, and decompression of the carpal tunnel will usually alleviate median nerve compression at this site.⁵ Haemodialysis and renal transplantation have been used in the management of renal failure.^{3,5}

We report the case of a man, first diagnosed as having primary systemic amyloidosis 14 years ago, who has had several complications that required surgical intervention.

Case report

A 63 year old man was referred in June 1972 with an elevated erythrocyte sedimentation rate (ESR). He had had a long history of back pain following a blast injury sustained in World War II. He had attended a spa in Central Europe where he was found to have a high ESR on routine screening.

On his return to England an upper abdominal mass was found. Investigation revealed an ESR of 60 mm/h and an iron deficient anaemia with an haemoglobin of 12 g/dl. A barium enema suggested that the abdominal mass was a carcinoma of the transverse colon (Figure 1). At laparotomy the tumour was found to involve adjacent organs necessitating an *en bloc* resection of the transverse colon, tail of pancreas, spleen and a loop of small bowel. Histological examination showed the tumour to consist of amyloid, situated mainly in the submucosa, but involving the full thickness of the bowel wall. Further investigations showed that he had normal levels of IgM (1.10 g/l; normal range 0.47–1.7 g/l) and IgG (8.2 g/l; normal range 5–16 g/l) and a low level of IgA (0.87 g/l; normal range 1.25–4.25 g/l) with no evidence of a monoclonal gammopathy. He made an uneventful post-operative recovery and was discharged from hospital. His ESR subsequently returned to normal.

He remained well for the next 6 years but presented

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Figure 1 Barium enema showing lesion involving the mid-transverse colon, reported as carcinoma (arrowed).

again in December 1978 with a 6 month history of recurrent subacute small bowel obstruction. On examination he was found to have a distended abdomen and several intra-abdominal masses were palpable. A full blood count, serum urea and electrolytes and liver function tests were normal. The ESR was again elevated at 54 mm/h and so was the plasma viscosity at 1.98 cP (normal range 1.5–1.72 cP). Plain radiography revealed fine snow storm calcification throughout the abdominal cavity. An intravenous pyelogram revealed a non-functioning right kidney and calcification of the left renal cortex with some evidence of lower ureteric obstruction (Figure 2). A DTPA renogram confirmed the absence of renal function of the right kidney and some degree of obstructive uropathy of the left kidney. There was only a trace of protein in the urine and blood urea and creatinine levels were normal. The serum total proteins and albumin levels were normal and so were the serum IgG and IgA levels, but the serum IgM was elevated (5.2 g/l). Electrophoresis showed paraprotein in both serum and urine and immuno-electrophoresis showed it to be lambda IgM type. There was no Bence-Jones proteinuria. Bone marrow examination showed a preponderance of lymphocytes (12% of all cells) and

Figure 2 Intravenous pyelogram showing non-functioning right kidney and calcification of the left renal capsule. There is some fullness of the calyces and a little dilatation of the left ureter throughout suggestive of distal ureteric obstruction. Note the fine snow storm calcification.

no evidence of a plasmacytoma. At laparotomy numerous ovoid tumours of amyloid were found in the abdominal cavity, many of which were easily removed. The tumours were of wax-like appearance and consistency. Histological examination confirmed that the tumours were composed of massive deposits of amyloid, similar in appearance to that found in 1972 but with less cellular infiltrate.

As a result of the bone marrow findings he was given eight 2-week courses of chlorambucil in the hope that it might reduce the production of IgM and subsequent deposition as amyloid. The serum paraprotein band gradually disappeared and was absent by the end of 1979. His blood count remained stable throughout the course of treatment.

In October 1979 he developed severe pain localized to the lower thoracic spine. Plain radiology of the thoracic spine showed partial collapse of D8 and D9

Figure 3 Lateral view of the thoracic spine showing partial collapse of the bodies of D8 and D9 vertebrae.

Figure 4 Plain abdominal X-ray view showing the marked increase in snow storm calcification.

vertebrae (Figure 3). Tomograms showed partial collapse of the body of D9 with abnormal texture throughout the body and extending into the pedicle, associated with bilateral paravertebral soft tissue masses. During the course of these investigations he developed ataxia of the right leg. On examination there was loss of vibration sense and diminished reflexes below the knee but no evidence of posterior column loss. Myelography revealed total block of the upward passage of myodil at the lower border of D9 associated with further collapse of the vertebral body. Plain abdominal radiology revealed a considerable increase in the snow storm calcification (Figure 4). A technetium 99m bone scan showed an area of increased uptake in the region of the ninth thoracic vertebra. Diffuse areas of abnormal uptake were also demonstrated in the abdominal wall and pelvis corresponding to new amyloid deposition. No particular

increase in cardiac or renal uptake of technetium was noted at this time. Exploration of the thoracic spine revealed tumour arising from the body of D9 and extending into posterior arch and the paraspinal muscle mass giving rise to cord compression. A wide laminectomy of D8 to 10 was performed and the tumour biopsies which showed amyloidoma of bone. He underwent post-operative radiotherapy of the spine and made a full neurological recovery. In view of the good clinical response it was decided to give radiotherapy to the amyloid deposits in the abdomen and pelvis. This resulted in partial shrinking of the abdominal masses.

He presented again in March 1982 with a painful abdominal mass and plain radiography showed small bowel obstruction and increased abdominal calcification. At laparotomy further amyloid tumours were removed with symptomatic improvement.

In September 1983 he became unwell and lost approximately eight kilograms in weight. He developed an iron deficiency anaemia (Hb = 10.7 g/dl) and had a raised plasma viscosity (1.9 cP). A bone marrow sample was found to be grossly hypocellular, probably secondary to radiotherapy, but there was no evidence of a plasmacytoma. He gradually improved on conservative management and remained well until July 1984 when he once again developed painful abdominal masses giving rise to subacute small bowel obstruction, that required excision. A repeat intravenous pyelogram showed increased hydronephrosis of the left kidney from extrinsic ureteric compression. Although the blood urea and creatinine levels were both elevated in the early post-operative period, both

returned to normal. Further investigations failed to reveal any evidence of a monoclonal gammopathy.

An additional finding has been progressive ECG changes of anterior hemiblock and progressive T wave inversion (first noted in 1974) and associated with infrequent brief episodes of palpitations. Although no tissue diagnosis is available these findings are consistent with cardiac amyloidosis. Tests of liver function show some abnormality suggesting hepatic infiltration.

The patient currently leads an active working professional life.

Discussion

Primary systemic amyloidosis (AL) is defined as amyloidosis occurring without evidence of preceding or co-existing disease except myeloma.³ It is characterized by extracellular tissue deposits of an abnormal protein made from immunoglobulin light chains. The deposits, which may be localized or systemic in distribution, interfere with physiological processes by replacing normal tissue and so affecting organ function. Systemic amyloidosis (AL) is now the most common presenting form of amyloidosis in the Western World, and up to half of the cases are associated with a plasmacytoma, although only 6 to 15% of cases of myeloma are associated with amyloidosis.⁹

Amyloid is diagnosed histochemically by positive staining with Congo red and identification of the amyloid fibril type may be undertaken using the potassium permanganate method.¹⁰ Tissue specimens obtained from patients with reactive systemic amyloidosis containing the AA-type fibrils lose the capacity to stain with Congo red following incubation with potassium permanganate. In contrast, tissue from patients with primary systemic amyloidosis with AL-type fibrils as well as tissue from patients with certain types of localized amyloidosis will stain with Congo red despite pre-incubation with potassium permanganate. Other more complex methods involving immunohistochemical techniques are also available.^{11, 12} In the case reported here, the diagnosis was first established before the availability of these techniques, but the clinical picture is that of (primary) systemic amyloidosis of the AL-type. Nevertheless it is recommended that identification of fibril type should now be routinely undertaken, particularly as reactive systemic amyloidosis (AA-type) carries a much better prognosis than systemic amyloidosis of the AL-type.²

Involvement of the gastrointestinal tract is common in systemic amyloidosis, with reported incidences from 70%¹³ to almost 100%¹⁴ although clinical manifestations are infrequent.¹⁵ Extensive deposition of amyloid in the bowel large enough to mimic a tumour is a most unusual presentation.¹⁶ There are several reports of

amyloid tumours in the stomach¹⁷⁻¹⁹ and small intestine²⁰ presenting thus. Only three cases have been reported as occurring in the colon: one was a polyp of localized amyloid in the sigmoid colon,²¹ another was a polyp in the rectum of a man with systemic amyloidosis²² and the third case was a mass in the descending colon in a patient with myeloma.¹⁶ In each case the presenting feature was of rectal bleeding or melaena. Our patient did not admit to episodes of bleeding, although the iron deficiency anaemia present at the time of diagnosis may be indicative of occult bleeding.

Multiple operations for the re-accumulation of peritoneal amyloid tissue have not previously been reported. In our patient it is presumably related to his long survival. At laparotomy he was noted to have very extensive amyloid deposits throughout the abdomen but despite this he never showed evidence of malabsorption or a motility disorder which are the more common gastrointestinal presentations of amyloid.^{1, 3}

Amyloid deposits are known to contain calcium and soft tissue scanning after injection of technetium-99 m pyrophosphate or disphosphonate may help in defining the extent of system involvement.⁵ This was illustrated in our patient by the diffuse uptake of technetium on a bone scan in 1979. This corresponded to the widespread abdominal calcification visible on plain radiographs. Such calcification has only been reported in a few conditions: tuberculous peritonitis, pseudomyxoma peritonei, haemangiomatosis and oil granulomas of the peritoneum.²³ It has not been previously described in the literature on amyloid disease.

Renal involvement occurs in most patients with systemic amyloidosis resulting in non-selective proteinuria and progressing to the nephrotic syndrome in approximately 30% of cases.³ In the present case the cause of impaired left renal function was largely due to extrinsic compression of the ureter causing a progressive obstructive uropathy and almost certainly due to retroperitoneal amyloid deposits. Some renal amyloid involvement may have also occurred as suggested by capsular calcification, although this was never severe as no more than intermittent traces of protein were ever detected in the urine. The cause of the non-functioning right kidney is not known but this may also have been due to an obstructive uropathy. Enhanced uptake of technetium-99 m by the kidneys might suggest renal amyloid involvement but this was not reported as such.

Cardiac infiltration by amyloid is also common in patients with systemic amyloidosis.^{2, 3} Although it was considered that the patient reported here had such involvement this never progressed to congestive cardiac failure. No increase in technetium-99 m uptake by the heart was noted in this case which may have

confirmed cardiac amyloid but this is not always diagnostic²⁴ and echocardiography is considered to be more sensitive.⁵

Compression of peripheral nerves by amyloid deposits is not uncommon, with carpal tunnel syndrome occurring in approximately 20% of cases of systemic amyloidosis.⁴ Spinal cord compression by amyloid tissue is rare in the absence of myeloma, with only two cases previously recorded.^{25, 26} In this case, although there was obvious vertebral collapse, the cause of the spinal cord compression was a mass of amyloid tissue within the vertebra and the expanded bone surrounding it. Involvement of the skeletal system with amyloid is not uncommon pathologically, but is rarely observed clinically.²⁷ The diagnosis of amyloid is usually made before the appearance of skeletal abnormalities. Radiographic evidence of disease has, however, been shown in 20% of cases.³ The most common finding is of osteoporosis, with or without evidence of fracture or bony collapse, but one third of cases will show osteolytic lesions, in which case there is usually an underlying plasmacytoma.³

Treatment of amyloidosis remains unsatisfactory. Cytotoxic drugs, colchicine and dimethylsulphoxide have been tried with little effect on the mortality of the disease.⁵ Radiotherapy is indicated in the treatment of myeloma deposits²⁸ but has not been used in the management of amyloid causing cord compression as in this case. Both the radiotherapy and chlorambucil therapy resulted in some objective improvement of this patient's condition, but once treatment stopped the amyloid began to re-accumulate. We would stress that while medical treatment remains relatively ineffective, prognosis is usually uncertain and surgery can play an important role in palliation in selected cases.

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