

# Dysphagia, sicca syndrome, chronic non-infectious diarrhoea – dominant symptoms of systemic AL amyloidosis

## A case report

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**Abstract.** *The presented case report shows that gastrointestinal symptomatology can be the dominant and sometimes the only clinical manifestation of systemic AL amyloidosis. One should think of this disease, because only early diagnosis can ensure a promising outcome of the treatment.*

**Key words:** *systemic AL amyloidosis, neuromuscular disorder of the oesophagus, diarrhoea, sicca syndrome, peripheral neuropathy*

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**Souhrn.** *Prezentovaná kazuistika ukazuje, že gastrointestinální symptomatologie může být dominantní a někdy jedinou klinickou manifestací systémové AL amyloidózy. Na toto onemocnění je třeba pomyslet, protože pouze včasná diagnóza dává nemocnému naději na možnou úspěšnost léčby.*

**Klíčová slova:** *systémová AL amyloidóza, neuromuskulární porucha jícnu, průjem, sicca syndrom, periferní neuropatie*

Systemic AL amyloidosis is a disorder characterized by accumulation of insoluble fibrillar protein in beta pleated sheet configuration, which is called amyloid, in the tissues. Accumulation of amyloid occurs extracellularly and initially perivascular deposition can be

found. In systemic AL amyloidosis monoclonal Ig light chains, usually of lambda type, secreted by abnormal clones of plasma cells, are the precursors of amyloid. These soluble light chains (or their fragments) circulate in the bloodstream, then move out of the blood ves-

sels into the organs and tissues, where their aggregation into insoluble amyloid deposits occurs (3). Amyloid deposits contain three components: a) 90 % of the amyloid material are amyloid protein fibrils with their tertiary structure “beta-pleated” sheets (where the binding sites for Congo red are situated); b) the deposits contain amyloid P (pentagonal) component; and c) sulfated glycosaminoglycans. Deposits of amyloid cause enlargement of the organ and finally reduction of its function. Amyloidosis can be associated with multiple myeloma or monoclonal gammopathy of undetermined significance.

### Case report

A sixty-year-old male patient had been – with the

exception of psoriasis vulgaris – healthy for the whole of his life, till March 2004, when the diagnosis monoclonal gammopathy of undetermined significance was determined. He was admitted to our department in April 2005 for the first time. Weight loss (15 kilograms during 2 months), whole day fatigue, swallowing difficulties, dryness in the oropharynx, reflux of food to the mouth after belching (especially at night), the need to drink after each mouthful, early satiety, dysphagia for solids, xerostomia, xerophthalmia and diarrhoea (not related to food or to time of day or to fasting) were some of his main complaints.

Because of sicca syndrome a Schirmer test took place and was bilaterally positive. Biopsy of the small salivatory glands was performed but with negative

Figure 1  
Toluidine blue-stained epoxy-resin semi-thin section of longitudinally orientated intestinal villus. The framed area is shown on the next figure under more powerful magnification. Original magnification 100x.

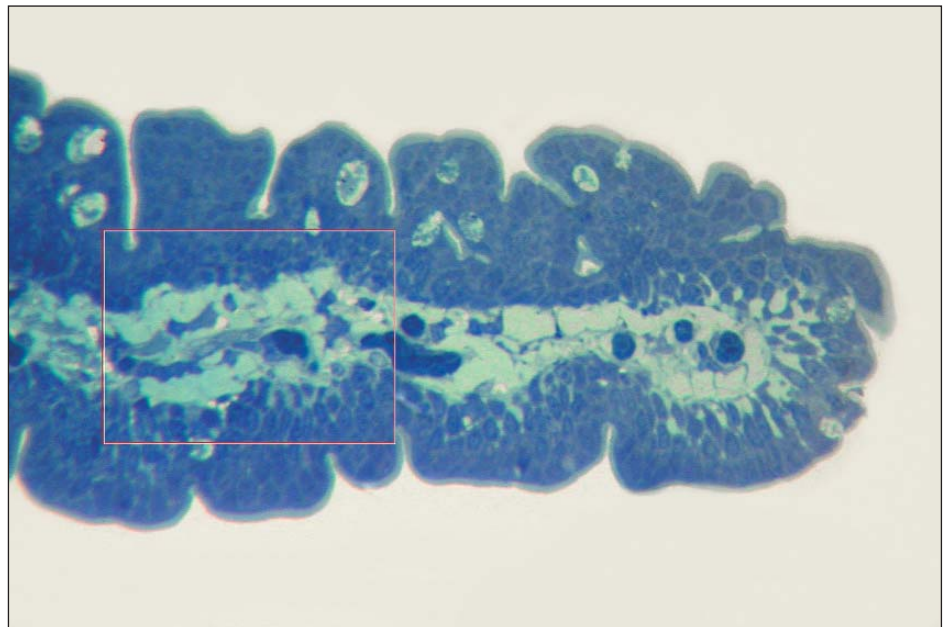
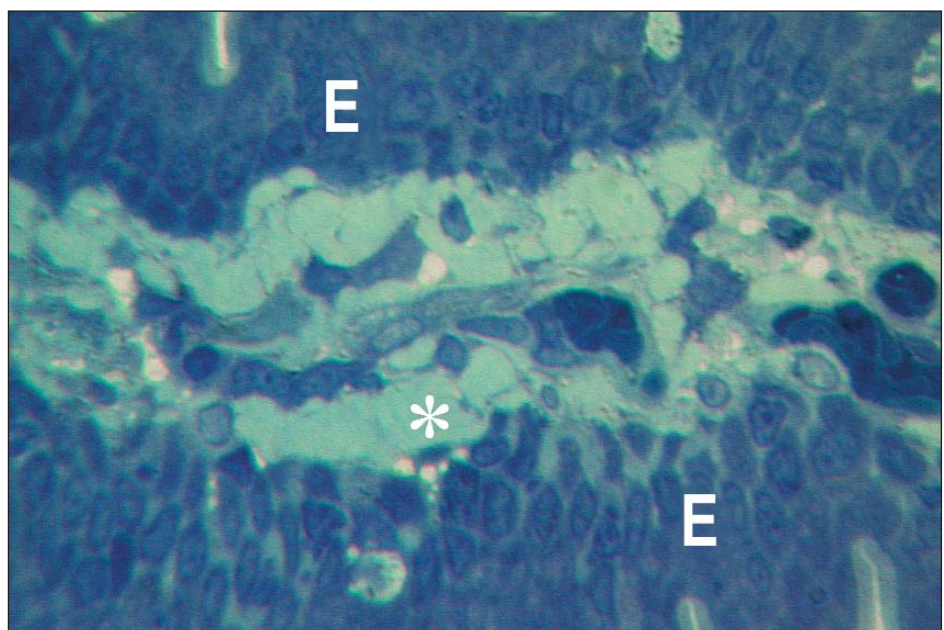


Figure 2  
The hyaline interstitial deposits marked with an asterisk. E – enterocytes. Original magnification 400x.





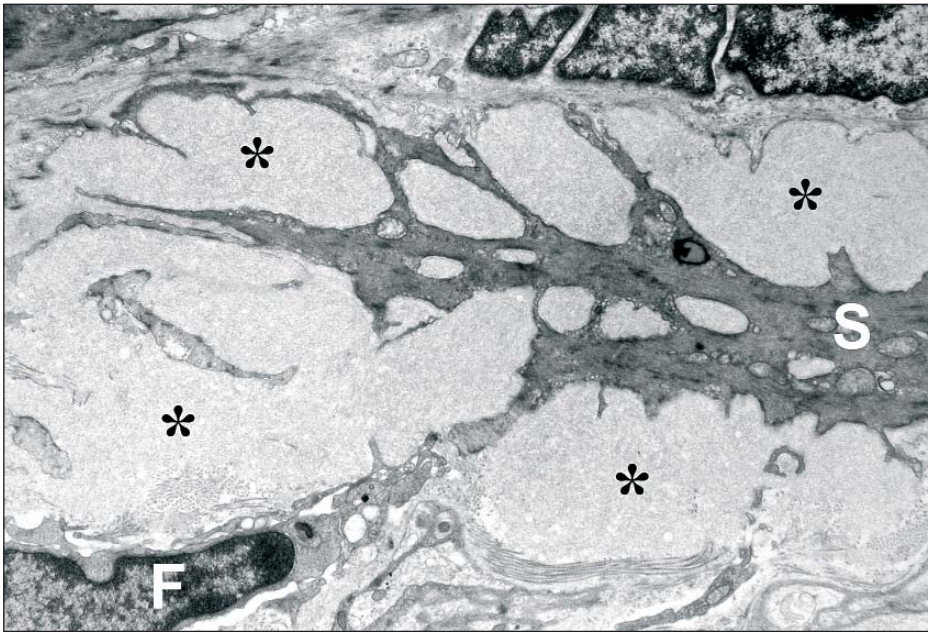


Figure 3  
Electron micrograph showing the amyloid deposits in the interstitium of the intestinal villus (asterisks). F - fibrocyte. S-smooth muscle cell. Original magnification 9,000x.

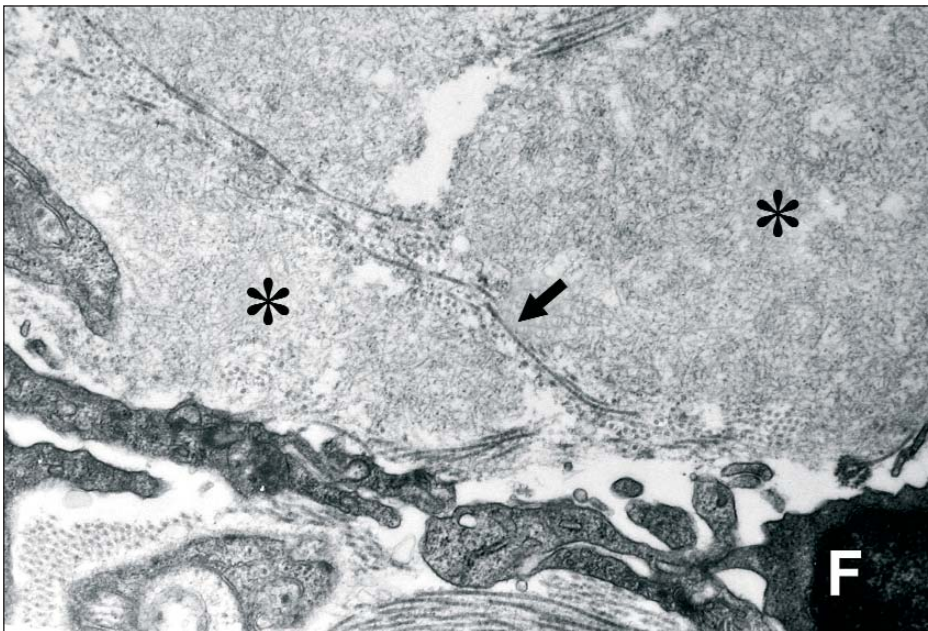


Figure 4  
Electron micrograph showing the difference between the collagen fibres (arrow) and 5 - 10 nm filaments of amyloid (asterisks) F-fibrocyte. Original magnification 20,000x.

result. Antibodies, which are usually found in Sjögren's syndrome (rheumatoid factors, antinuclear antibodies, ENA, SS-A/Ro, SS-B/La) were absent, so a diagnosis of Sjögren's syndrome was not confirmed.

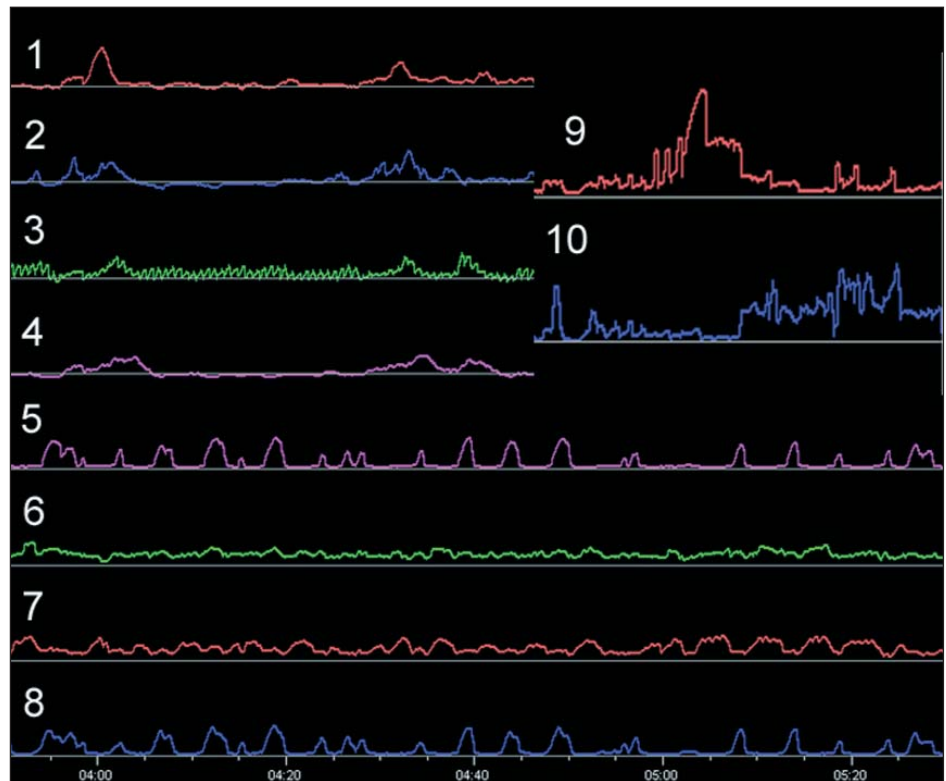
Due to dysphagia for solids our patient underwent gastroscopy, where reflux oesophagitis (stage 1 of Savary-Miller classification), mild soor of the oesophagus and delayed gastric emptying were found. Manometry showed a non-specific disorder of oesophageal motility (lower amplitude of the peristaltic waves, which were propulsive in majority). Decreased tonus of well-relaxed lower oesophageal sphincter and decreased tonus with mild disorder of relaxation of upper oesophageal sphincter were present (Fig. 5). Electrogastrography was performed, too, fas-

ting bradygastria and postprandial tachygastria were found. Colonoscopy was normal and no amyloid was found in the rectal biopsy (stained with Congo-red). No oxyphilic deposits were detected in the histological slides, so presence of paraamyloid deposits could have been excluded. In September 2005 push-enteroscopy with a biopsy of the duodenum took place. During the endoscopy no signs of amyloid deposition were detected, the anatomical structure of the bowel was well-preserved. It was very surprising, that the staining of the biopsy specimen with Congo-red (Maldyk) was negative, but microfibrils of amyloid were found by electron microscopy (Figs 1-4).

No pathology (osteolytic lesions) was found on chest X-ray. Electrocardiography showed inversion of T

Figure 5

**Oesophageal manometry. Non-specific oesophageal motor disorder.** Channels 1 – 4: the contractive activity after wet swallows (10 mL water): simultaneous, multipeaked contractions of low amplitude (24 mm Hg). Channels 5 – 8: lower oesophageal sphincter study: still normal values of the resting pressure (11 mm Hg) with complete relaxation (92 %). Channels 9 – 10: upper oesophageal sphincter study: decreased resting pressure (36 mm Hg), incomplete relaxation of the upper oesophageal sphincter (82 %).



waves in II, III and aVF leads. During the patient's last stay in our Department (October 2005) he underwent echocardiography, where symmetric hypertrophy of the left ventricle was described. MRI of the heart was done, too, concentric hypertrophy of the left ventricle and less important hypertrophy of the right ventricle were detected. This finding could be compatible with the diagnosis of primary amyloidosis. Dynamic electrocardiography showed paroxysmal atrial fibrillation, isolated atrial and ventricular extrasystoles. Presyncopal states – due to postural hypotension – were present in our patient, too (blood pressure was usually about 90-100/50-60 mm Hg). No rapid change of liver enzymes occurred, only mild elevation of ALT (1.22  $\mu$ kat/L) and alkaline phosphatase (3.12  $\mu$ kat/L) was present. In autumn 2005 abdominal ultrasound – just as physical examination – showed hepatomegaly, enlargement of the prostate and new mild ascites. Finally liver biopsy was realized. The tissue stained positively with Congo-red and AL type of amyloidosis was confirmed by immunohistochemical methods with the majority of lambda light chains (kappa light chains were present only in minority). No renal pathology was present, abdominal ultrasound described normal anatomy of both kidneys. No elevation of serum urea and creatinine was found. Only mild proteinuria was present during patient's last stay (October 2005: proteinuria 0.55 g/L). Other laboratory tests showed anaemia (haemoglobin

94 to 98 g/L), hypokalaemia (3.3 to 3.4 mmol/L without any substitution), hypoproteinaemia (total protein 61.6 g/L, albumin 29.7 g/L). In the immunological tests mild elevation of IgG (16.30 g/L) and mild suppression of IgA (0.96 g/L) and IgM (0.93 g/L) were found. The presence of IgG kappa in the serum was confirmed by immunofixation (in the concentration of 14.2 g/L). Bence-Jones protein was present in the concentration of 0.4 g/L in the urine, too. In the trephine biopsy no signs of multiple myeloma were discovered.

Our patient had complained about paraesthesias and numbness in the distal parts of the lower and upper limbs since April 2005. Neurological investigation and electromyogram were performed, peripheral sensory polyneuropathy of upper extremities and axonal motoric polyneuropathy of the lower limbs were detected. Carpal tunnel syndrome was present bilaterally. When the diagnosis of primary amyloidosis had been determined from the liver biopsy, clinical haematologists decided systemic chemotherapy (doxorubicin and dexamethasone) should be started as a treatment. The tolerance to chemotherapy was good and autologous stem cell transplantation will take place in the case of our patient.

## Discussion

We present an unusual case of systemic AL amyloidosis associated with monoclonal gammopathy of

undetermined significance, where the majority of gastrointestinal symptoms was not caused by amyloid infiltration of organs themselves, but by peripheral autonomic neuropathy.

Amyloidosis is a group of diverse diseases, characterized by extracellular amyloid deposits. The classification of amyloidosis (2) depends on the distribution of amyloid (localized or systemic amyloidosis), the presence of a pre-existing disease (systemic AL or systemic AA amyloidosis) and the chemical type of insoluble amyloid fibril. Nowadays systemic AL amyloidosis is the most common type of amyloidosis in the western countries. In the Third World systemic AA amyloidosis is more common, because long-standing inflammatory diseases (such as tuberculosis, malaria, syphilis, leprosy, osteomyelitis and bronchiectasis) are followed by this secondary form of amyloidosis (6). In western countries systemic AA amyloidosis is usually associated with rheumatoid arthritis or ankylosing spondylitis. Systemic AL amyloidosis is a disease of adulthood (1). The peak of occurrence is around the age of 60 – 65 (10), the predominant sex is male (male : female ratio 2:1) (6).

Deposits of amyloid can be found in practically any organ of the body, therefore clinical presentation is variable. When patients are classified as having a dominant organ manifestation, cardiac amyloid is the most common (37.4 %), followed by renal amyloidosis (27.8 %) and amyloid peripheral neuropathy (15.3 %). The presence of amyloid in gastrointestinal tract is found in approximately 8 % (6). Oral manifestations of systemic AL amyloidosis have been confirmed in 39 % of patients with this diagnosis. The oral symptoms of systemic AL amyloidosis are variable – dryness, pain and dysphagia. Ecchymoses, petechiae and purpura may be detected in the oral cavity (1). Macroglossia, which was not found by our patient, is a highly specific symptom for systemic AL amyloidosis (does not occur in familial, secondary or senile systemic amyloidosis). Enlargement of the tongue is seen in approximately 10 % of patients (6). Our patient complained about xerophthalmia and xerostomia, so the sicca syndrome was present. Xerostomia occurs, when minor salivatory glands are infiltrated by amyloid. It was interesting, that histological investigation of minor salivatory glands biopsy was negative, autonomic neuropathy might have been manifested in this way. Labial salivatory glands biopsies seem to be more reliable test for the diagnosis of sys-

temic AL amyloidosis (e.g. in comparison with abdominal fat aspirate) (5).

Oesophageal and gastrointestinal disorders in amyloidosis may result from either musocal infiltration or neuromuscular infiltration (3). As mentioned above, our patient had swallowing difficulties, too. It is very important to mention, that no infiltration of mucosa was detected during the endoscopic investigation and biopsy of the oesophageal mucosa was negative, too. The aetiology of patient's dysphagia might have been due to infiltration of autonomic nerves by amyloid, too. Amyloidosis can cause dysphagia by selective impairment of the inhibitory neural pathway to the lower oesophageal sphincter, the hypertensive sphincter can be found by manometric studies (11). Amyloid deposition in the gastrointestinal system seems to be less common in systemic AL amyloidosis (than in systemic AA amyloidosis) (3). Eight percent of patients with primary amyloidosis have gastrointestinal amyloidosis diagnosed by bioptic examination, but only 1 % of them have symptomatic gastric amyloidosis (14). In the gastrointestinal tract the most common sites of amyloid infiltration by systemic AL amyloidosis are the descending duodenum (100 % – just as was the case in our patient), the stomach and colorectum (more than 90 %) and the oesophagus (about 70 %) (3). The descending colon and rectosigmoid portion are the most frequent locations of amyloid infiltration in the large bowel. Endoscopic investigation can show granular appearance, erosions, mucosal friability, polypoid protrusions and thickening of the wall (3).

Gastrointestinal amyloidosis is usually manifested by one of following four disorders:

- 1) Chronic intestinal dysmotility (usually caused by neuromuscular infiltration), which leads to dysphagia, gastroparesis and constipation. A case of paralysis of digestive tract caused by amyloid deposition within the myenteric plexus was described, too, this deposition resulted in acute intestinal obstruction, prompt laparotomy took place, but no aetiology was found (11). Dysmotility can cause a rapid intestinal transit, so the diarrhoea – like by our patient – can occur. Sometimes intermittent diarrhoea is considered to be a symptom of inflammatory bowel disease before a histological and immunohistochemical examination, which leads to a diagnosis of systemic AL amyloidosis (23). Diarrhoea can be treated with lo-



peramide, diphenoxylate or with injections of long-acting octreotide. Sometimes parenteral nutrition has to be used (6).

- 2) Gastrointestinal bleeding due to mucosal lesions or vascular friability. It is well known that there is a higher incidence of gastrointestinal tract bleeding in patients undergoing autologous stem cell transplantation for systemic AL amyloidosis (9).
- 3) Protein-losing gastroenteropathy, leading to hypoalbuminaemia and oedema, can occur, too (3).
- 4) Malabsorption, caused by mucosal infiltration or bacterial overgrowth can be found in many cases of primary amyloidosis. Diarrhoea, steatorrhoea, weight loss (with median of 15 kilogrammes – just as was the case in our patient), anorexia, dizziness, orthostatic hypotension belong to the most common symptoms (7).

Obstructing masses can sometimes also be present, in one patient an intestinal subocclusion was observed and endoscopic investigation showed a stenosing neoplasm. Endoscopy was followed by segmentary colectomy of the transverse colon, after this the correct diagnosis was determined by histological and immunohistological methods (18). A small bowel obstruction, caused by encapsulating peritonitis, was described, too (8). Descending and rectosigmoid colon are the most common locations of amyloid infiltration in the large bowel. Usually one of five pathological findings in the large bowel (or their combination), caused by infiltration of amyloid, can be detected by radiologic methods: luminal narrowing, loss of haustrations, thickened mucosal folds and mucosal nodularity or ulcerations (23).

The most frequent clinical finding of hepatic primary amyloidosis is hepatomegaly (about 81 %), ascites (42 %) and oedema (26 %) (3). Usually only elevation of alkaline phosphatase of all liver enzymes is seen. Involuntary weight loss, fatigue, early satiety and nausea were the most common symptoms of hepatic amyloidosis occurred by our patient.

With the hepatic and splenic amyloidosis factor X deficiency is associated. When the value of this factor is below 25 %, serious bleeding starts.

When amyloid infiltrates the heart, it becomes enlarged and arrhythmias can appear. Paroxysmal fibrillation, supraventricular and ventricle extrasystoles were detected during dynamic electrocardiography by our patient. Echocardiography (just like MRI) showed concentric left ventricular hypertrophy, which

might be compatible with the diagnosis of systemic AL amyloidosis and could lead to poor diastolic filling. The collapses could have originated here (not only from the autonomic neuropathy). It is well known that survival in cardiac primary amyloidosis partially refers to the level of serum cardiac troponin (4).

Renal amyloidosis is the second most common type of amyloidosis (after cardiac one) (6). Usually elevation of serum creatinine level can occur (not present in our patient) and non-selective proteinuria (20), caused by amyloid deposits, which damage glomerular basement membrane. Mild proteinuria (0.55 g/L) was detected in our patient, but no nephrotic syndrome occurred. Because of pre-existing benign hypertrophy of prostate we thought at first urinary retention was caused only by this disorder, however amyloid autonomic nerve infiltration could play a role, too (6).

Peripheral neuropathy with its autonomic component can be easily misdiagnosed with neuropathy, associated with diabetes mellitus (6). The neuropathy is usually seen in the lower limbs at first. Characteristic features – by our patient too – are paraesthesia, numbness, burning in the distal parts, aching pains with electrical sensations, loss of thermal sensation, pain in the distal limbs and carpal tunnel syndrome (this syndrome was bilaterally positive by our patient), usually caused by deposits of amyloid in flexor retinaculum (22). The diagnosis of peripheral neuropathy is confirmed either by electromyography or by biopsy of the sural nerve (6). It is important to maintain, that sural nerve biopsy is less sensitive than was believed until now (21). Peripheral neuropathy combined with production of monoclonal protein is pathognomonic for systemic AL amyloidosis or amyloidosis associated with multiple myeloma or Waldenström macroglobulinaemia (13). Sometimes cranial neuropathy seems to be a major manifestation of systemic AL amyloidosis (22).

Mucocutaneous involvement is seen in 30 – 40 % of patients with systemic AL amyloidosis. The most common findings are petechiae, ecchymoses, macules, papules, and dystrophic nail changes (6). Diminished functioning of the adrenal glands (Addison disease) and other endocrine glands (thyroid gland) can be seen. Due to diffuse vascular involvement, claudication, muscular pseudohypertrophy, muscular atrophy (where creatine kinase may be elevated) and painful joints can be present.

When some of the outlined symptoms and disor-

ders are found out, immunofixation of the serum and of the urine should be realized. Immunofixation is the best sensitive and non-invasive screening test. Then bone marrow biopsy is usually performed to exclude the presence of multiple myeloma. This biopsy might be combined with subcutaneous fat biopsy. Sometimes other biopsies are required, e.g. rectal, duodenal, jejunal, liver, endomyocardial, skin, renal, minor salivatory glands and biopsy of the sural nerve. A new nephelometric technique was found, free light chains can be detected by this method. The amyloid P component, which is present in every type of amyloid, can be radiolabelled with iodine to detect deposits of amyloid (6). In histological slides stained with haematoxylin and eosin, homogenous pink extracellular material is observed. In slides stained with Congo red, orange colour by light microscopy and green

birefringence is recognized by polarizing microscopy. Deposits of amyloid are also able to bind thioflavine T, which leads to an intense yellow-green fluorescence (3). By electron microscopy, non-branching fibrils, 7.5 – 10 nm in diameter (demonstrated on the figures) are found.

The most common treatment for primary amyloidosis is combination of melphalan and prednisone. Treatment with melphalan, followed by bone marrow stem cell rescue has proven effective. Before stem cell transplantation VAD (vincristine, anthracycline and dexamethasone) regimen is used as an induction treatment (6,12).

However, it is not common to think about diagnosis of systemic AL amyloidosis, when “only” gastrointestinal symptoms are present, but prognosis, especially by this disease, depends on early diagnosis.

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