Severe gastrointestinal involvement in an adult female patient with chronic mucocutaneous candidiasis

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Kopáčová M, Rejchrt S, Repák R, Kopecký O, Špaček J, Nožička Z, Koudelková V, Žák P, Bureš J. Severe gastrointestinal involvement in an adult female patient with chronic mucocutaneous candidiasis. Folia Gastroenterol Hepatol 2005; 3 (2): 62 – 66.

Abstract. *Chronic mucocutaneous candidiasis is a condition of heterogeneous causes in which there is chronic infection of mucous membranes, skin, and nails with fungi of Candida species. We present a case of severe multiple gastrointestinal involvement in an adult female patient with a sporadic inherited form of chronic mucocutaneous candidiasis. Tight stenosis of the distal oesophagus, stenosis of the duodenal bulb (with Helicobacter pylori negative chronic ulcer) and diffuse inflammatory involvement of the large bowel with a stenosis of the sigmoid colon were found. During the next three years the patient underwent 31 bougie dilatations of the oesophageal stenosis with satisfactory effect. The patient refused allogeneic stem cell transplantation. Final pulmonary embolism led to her death (at the age of 45).*

Key words: *mucocutaneous candidiasis, gastrointestinal involvement, oesophageal stenosis, duodenal stenosis, colitis, endoscopic dilatation*

Kopáčová M, Rejchrt S, Repák R, Kopecký O, Špaček J, Nožička Z, Koudelková V, Žák P, Bureš J. Těžké postižení gastrointestinálního traktu u dospělé pacientky s chronickou mukokutánní kandidózou. Folia Gastroenterol Hepatol 2005; 3 (2): 62 – 66.

Souhrn. *Chronická mukokutánní kandidóza je onemocnění z různorodých příčin, při kterém dochází k chronické infekci sliznic, kůže a nehtů kandidami. Tato kazuistika prezentuje případ dospělé pacientky se sporadickou vrozenou formou chronické mukokutánní kandidózy s těžkým postižením gastrointestinálního traktu. Byly zjištěny těsná stenóza jícnu, stenóza bulbu duodena (s chronickým Helicobacter pylori negativním vředem) a difúzní zánětlivé postižení tlustého střeva se stenózou sigmatu. V průběhu tří let nemocná podstoupila 31 bužiových dilatací stenózy jícnu s uspokojivým efektem. Pacientka odmítla alogenní transplantaci kmenových buněk. Nemocná zemřela na plicní embolizaci (ve věku 45 let).*

Klíčová slova: *mukokutánní kandidóza, gastrointestinální postižení, stenóza jícnu, stenóza duodena, kolitida, endoskopická dilatace*

Chronic mucocutaneous candidiasis is a condition of heterogeneous causes in which there is chronic infection of mucous membranes, skin, and nails with fungi of Candida species. Both primary (inherited) and secondary (acquired) systemic candidiasis are mostly due to T-cell-associated immunodeficiency (dysfunction). The gastrointestinal manifestations of chronic mucocutaneous candidiasis include oral ulcers, oesophageal disease (strictures, dysphagia, rupture), gastritis, iron deficiency, diarrhoea and malabsorption (9,10). We present a case of severe multiple gastrointestinal involvement in an adult female patient with a sporadic form of chronic mucocutaneous candidiasis.

Case report

A 42-year-old woman was first admitted to our Department in June 1998 because of dysphagia and cachexia. She had no familial history of immunodeficiency. Since her early childhood she had been suffering from recurrent respiratory and urinary infections, from chronic mucocutaneous candidiasis (oral mucosa, skin, fingernails and toenails were affected), recurrent oral aphthous lesions, chronic seborrhoic dermatitis of the scalp, chronic angular stomatitis, chronic keratoconjunctivitis and persistent skin lesions. She had had no indices of mental retardation, there were neither neurological abnormalities nor signs of myopathy. The patient had had regular menstruation (despite of cachexia) and no gynaecological complains. She had been suffering from diarrhoea and abdominal cramps, these symptoms worsened one month before admission together with a new onset of dysphagia for solids and low-grade fever. The patient was of small stature (152 cm), cachectic, weighting 18.5 kg (body-mass index 8.0 kg/m^2). She was of childlike appearance, with a keel-shaped face, nasal prominence, prognathia with small mandible (with very limited motion in the temporo-mandibular joints) and protuberant ears. There were evident signs of chronic oral and nails candidiasis (Figs 1 and 2), confirmed by subsequent culture. In laboratory tests, there were severe iron-deficiency anaemia and borderline leukopoenia, evident signs of T-cell dysfunction (decreased CD-3+ T-lymphocytes, increased T-lymphocytes γ/δ), normal serum immunoglobulins concentrations, normal calcaemia (but metabolic bone disease) and normal thyroid function. HIV testing (1,2) was negative. Antibodies against endomysium and tissue transglutaminase were negative. Connective tissue disease was excluded, too. There was a severe proteino-energy malnutrition (with extremely low serum concentration of prealbumin and transferrin). Abdominal ultrasound showed moderate splenomegaly, gallbladder stones and nephrolithiasis. Tight stenosis of the distal oesophagus was found at

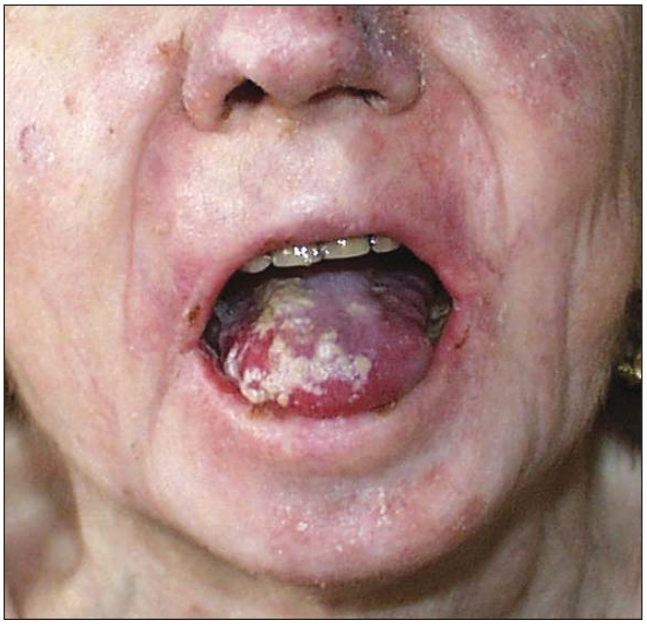

Figure 1 / Obr. 1
Chronic mucocutaneous candidiasis. Skin of the face and mucous membranes of the mouth are affected by severe chronic candidiasis.
Chronická mukokutánní kandidóza. Kůže obličeje a sliznice dutiny ústní jsou těžce postiženy chronickou kandidózou.

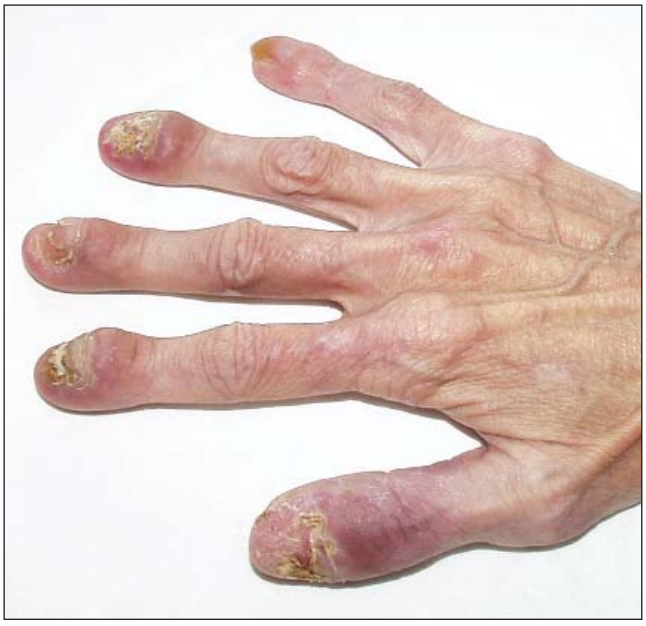

Figure 2 / Obr. 2
Chronic mucocutaneous candidiasis. Severe chronic mycosis of skin and nails.
Chronická mukokutánní kandidóza. Těžká chronická mykóza kůže a nehtů ruky.

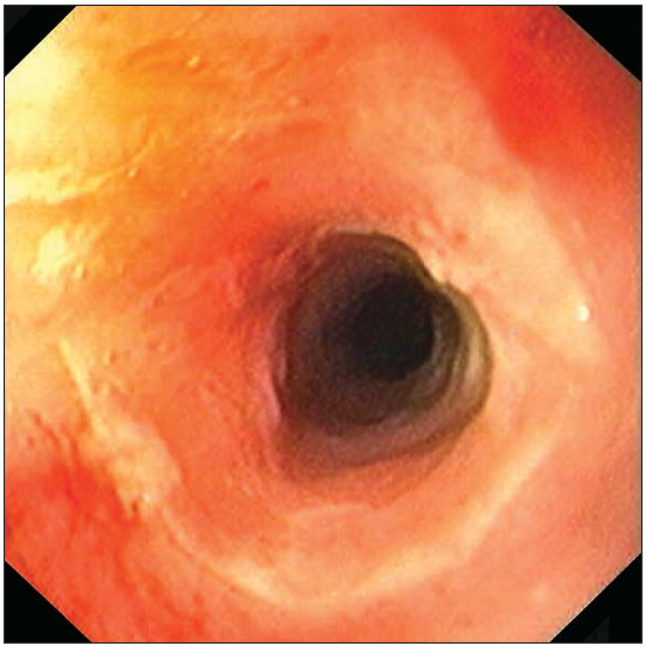

Figure 3 / Obr. 3
Tight stenosis of the distal oesophagus was found at endoscopy (5 mm in diameter, 10 mm in length).
Při endoskopii byla nalezena těsná stenóza distálního jícnu (průsvit 5 mm, 10 mm dlouhá).

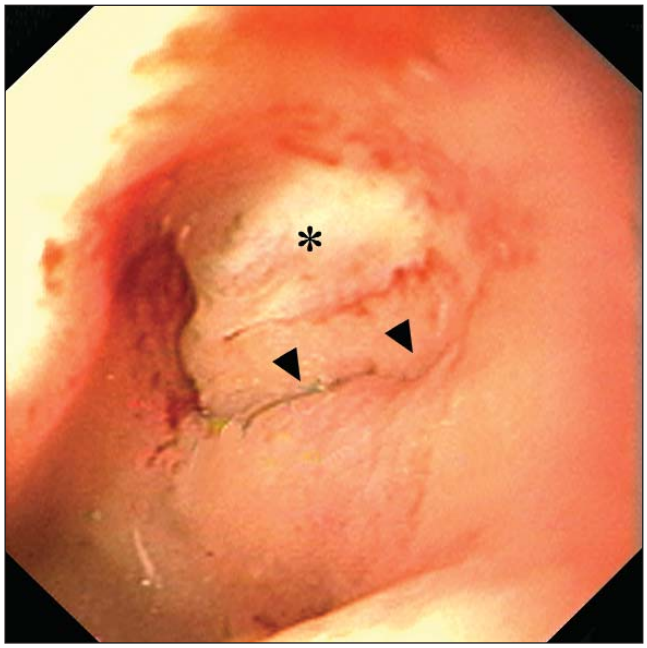

Figure 4 / Obr. 4
Tight stenosis of the duodenal bulb with chronic Helicobacter pylori negative ulcer (asterisk). The lumen is marked by arrowheads.
Těsná stenóza bulbu duodena s chronickým Helicobacter pylori negativním vředem (hvězdička). Lumen je označeno hroty.

endoscopy (5 mm in diameter, 10 mm in length), see Fig 3. After initial dilatation of the stenosis, it was possible to endoscope on, axial hiatal hernia, chronic Helicobacter pylori negative pan-gastritis (at histology) and tight stenosis of the duodenal bulb (with chronic ulcer) were found (Fig 4). The patient had been on painkillers (containing codeine and aspirin) that might be a worsening factor both to the oesophageal involvement and duodenal ulcer.

As it was not possible to pass the endoscope through the duodenal stenosis, a lever-operated capsule was introduced under fluoroscopic control to the proximal jejunum for a “blind” small bowel biopsy. Both standard optical histology and electron microscopy excluded coeliac disease (microvilli were preserved, only non-specific inflammatory changes were found in the mucosa and lamina propria). No bacterial infection and no parasites were found in stool samples with repeated tests. Tight sigmoid stenosis with ulcers and surrounding non-specific inflammatory changes was diagnosed at colonoscopy (Fig 5). The stenosis could not be passed by an endoscope through. Subsequent double-contrast barium enema revealed diffuse pan-colitis indicated by a marked loss of haustration and narrowing of the colon. No malignancy was found within a 3-year follow-up.

As dysphagia was a leading symptom, we started with bougie dilatations of the oesophageal stenosis with a significant subjective improvement, the patient was able to swallow both solids and liquids without any problems. Enteral nutrition, using a polymeric formula, was started by means of a fine-bore nasojejunal tube (introduced through the duodenal stenosis endoscopically). Several broad-spectrum antibiotics and both systemic and topical antimycotics (fluconazole, itraconazole, ketoconazole, natamycine) were administered. The patient was given proton pump inhibitors and supplemented with iron and vitamin D. Transfusions of deleucotized blood were given consecutively without any side-effect reaction. Intravenous immunoglobulin was administrated regularly twice a month. Treatment with immunostimulants was started, the so called “transfer factor” was given once every two weeks s.c. (transfer factor – transferendi factor humanus – is a dialysate of peripheral leukocytes of healthy blood donors). Thanks to his complex therapy, the general condition of the patient improved, she gained 13 kg within 9 months (from 18 to 31 kg; a body-mass index of 13.4 was reached). During the next three years the patient underwent 31 bougie dilatations of the oesophageal stenosis with satisfactory effects (the widest used bougie was 12.8 mm). We have had only one complication. There was

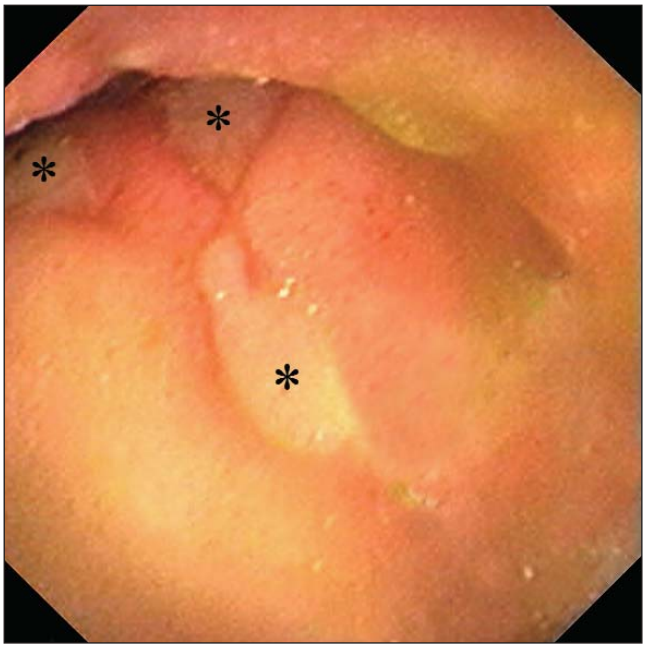

Figure 5 / Obr. 5
Tight sigmoid stenosis with multiple ulcers (asterisks) and surrounding non-specific inflammatory changes was diagnosed at colonoscopy.
Při koloskopii byla zjištěna těsná stenóza sigmatu s mnohočetnými ulceracemi (hvězdičky) a nespecifickými zánětlivými změnami.

a laceration of the oesophageal mucosa with oozing bleeding, which was solved endoscopically. Undergoing repeated dilatations (usually at 3-month intervals) the patient did not have any problems swallowing. Nevertheless, she continued to have repeated infections during this period, respiratory (pneumonia three times), urinary and ocular. The patient was considered to be a candidate for allogeneic stem cell transplantation. Unfortunately, her sister presented HLA incompatibility and an unrelated donor was not available in the first time period. Later the patient refused allogeneic stem cell transplantation.

The patient's last stay in our Department was in September 2001. She was admitted because of bilateral bronchopneumonia, urinary infection and exsiccation. Shortly after this admission sudden cardiac arrest occurred, successful cardiopulmonary resuscitation was performed. Then the patient was artificially ventilated for a month. Final pulmonary embolism led to her death.

Discussion

We present a case of severe multiple gastrointestinal involvement in an adult female patient with a sporadic form of chronic mucocutaneous candidiasis due to primary (inherited) T-cell immunodeficiency (disturbance of T-lymphocytes maturation and activation). In addition to early candidiasis, she had been suffering from recurrent respiratory and urinary infections since her early childhood, too. This patient had previously been treated elsewhere as severe combined immunodeficiency (SCID). SCID syndromes are a heterogenous group of disorders arising from a disturbance in the development and function of both T and B cells (1,2,22). However, laboratory criteria were not fulfilled in the presented case (i.e. CD3 < 10 %, CD16/56 < 2 % and CD19 > 75 %). And most of all, a patient with true SCID without bone marrow transplantation would not live till adulthood (2,6,7,21,22). The small stature and characteristic appearance of her face would resemble Bloom syndrome (12). However, she had no sun-sensitivity, presented normal serum immunoglobulines and developed no malignancy (up to her age of 45). Nijmegen breakage syndrome (13) was excluded because of lack of microcephaly and mental retardation.

Chronic mucocutaneous candidiasis is a rare syndrome that usually has its onset in childhood. Some patients have autosomal recessive polyglandular autoimmune syndrome type I (APECED syndrome) (9). Our patient had had no endocrine disorder (like hypoparathyroidism or adrenal insufficiency). Some patients with chronic mucocutaneous candidiasis have no associated diseases. An underlying T cell defect is thought to be responsible for the inability of these patients to eradicate Candida from mucous membranes and cutaneous structures (10) but not yet fully understood in details (4,14,17). No gene defect has as yet been identified in patients with chronic mucocutaneous candidiasis without endocrinopathy although occasional reports of multiple affected family members were published (14). Different classifications were proposed, for instance according to Coleman & Hay (3) there are sporadic forms, familial forms, a form associated with interstitial keratitis, and a form associated with thymoma.

Clinical manifestations of candidiasis include severe recurrent thrush, onychomycosis, vaginitis and chronic skin lesions. Visceral invasion is rare (9). Oesophageal stenosis is the most common gastrointestinal complication of chronic mucocutaneous candidiasis (15,20,23), diarrhoea and iron-deficiency anaemia are other possible features (9,23). The disease can be associated with a short stature and delayed puberty (23). Ketoconazole and fluconazole were reported to improve oesophageal stenosis in

mucocutaneous candidiasis (15,18,23). In other case reports, interleukin-2 (19), high-dose i.v. immunoglobulins (17) or transfer factor (11) induced marked regression in mucocutaneous candidiasis. In our case, antimycotics, transfer factor and i.v. immunoglobulins failed to improve gastrointestinal involvement substantially, but the oesophageal stenosis was satisfactory controlled by regular bougie dilatations for three years. Stenosis of the duodenal bulb and chronic duodenal ulcer were asymptomatic. There was no villi atrophy of the small bowel. Colonic stenosis has been described in SCID but not in mucocutaneous candidiasis (16). In our case, there was a diffuse inflammatory involvement of the large bowel with a tight stenosis of the sigmoid colon. Chronic pan-colitis was a cause of diarrhoea. Stem cell transplantation can be considered in severe chronic mucocutaneous candidiasis (5,8). In our case, a suitable donor was not available in the first time period, later the patient refused allogeneic stem cell transplantation.

Albeit being a palliative treatment, bougie dilatation is a feasible method that significantly improves the quality of life of patients with severe dysphagia due to tight oesophageal stenosis in chronic mucocutaneous candidiasis.

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